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Synthesis of Benz(f)tryptophan and Constrained Amino Acid Derivatives as Fluorescence Probes.

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SYNTHESIS OF BENZ[*F*]TRYPTOPHAN AND CONSTRAINED AMINO ACID DERIVATIVES AS FLUORESCENCE PROBES

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
COSY	^{1}H-^{1}H Correlation Spectroscopy
TSP	Sodium 3-trimethylsilylpropanoate-2,2,3,3-d_4
Hz	Hertz
MHz	Megahertz
s	singlet
d	doublet
dd	doublet of doublets
t	triplet
dt	doublet of triplets
q	quartet
m	multiplet
br s	broad singlet
GC	Gas Chromatography
MS	Mass Spectrometry
DCM	Dichloromethane
THF	Tetrahydrofuran
DMSO	Dimethylsulfoxide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMAP	4-Dimethylaminopyridine
Pd/C	Palladium on activated carbon
MeOH	Methanol
EtOH	Ethanol

DHA	Dihexachlorocyclopentadiene-Adduct
LDA	Lithium diisopropylamide
NBS	N-Bromosuccinimide
t-Boc	*tert*-Butyloxycarbonyl
Fmoc	9-Fluorenylmethyloxycarbonyl
deg	degree
mp	melting point
dec	decomposition
anh.	anhydrous
Calcd	Calculated
Anal.	Analysis

ABSTRACT

Constrained amino acids and benzannulated analogs of indole were synthesized as potential fluorescence probes of peptide structure.

1-Amino-2-(3-indolyl)-cyclohexane-1-carboxylic acid (W3) is a rotationally-restricted tryptophan analog whose C_α-C_β bond is part of a 6-membered ring. Friedel-Crafts reaction between α-hydroxycyclohexanone and indole affords 2-(3-indolyl)cyclohexanone which is further converted into its corresponding spirohydantoin derivative via Strecker reaction. Basic hydrolysis of this hydantoin derivative with $Ba(OH)_2$ in oxygen-free water at 250 °C in a Parr® high pressure bomb afforded the constrained tryptophan analog.

N-(*t*-Boc)piperidine-4-amino-4-carboxylic acid is a constrained Aib analog. Treatment of 4-piperidinone monohydrate hydrochloide with triethyl amine, catalytic amounts of N,N-dimethylamino pyridine and di-*tert*-butyl dicarbonate affords N-(*t*-Boc)-4-piperidinone which is transformed into its corresponding spirohydantoin derivative via Strecker reaction. This hydantoin derivative is fully reacted with di-*tert*-butyl dicarbonate and hydrolyzed with aq. 1N LiOH in THF to provide the desired α-amino acid product.

Benz[*f*]indole is synthesized via Batcho-Leimbruger reaction between 3-methyl-2-nitronaphthalene and a mixture of pyrrolidine/N,N-dimethylformamide dimethyl acetal followed by hydrogenation at 30 p.s.i.

3-Methyl-benz[*f*]indole is synthesized via palladium-catalyzed cyclization reaction between 3-bromo-2-aminonaphthalene and 1-trimethylsilyl-propyne in refluxing acetonitrile followed by reflux with HCl.

Progress towards the synthesis of benz[*f*]tryptophan using 3-bromo-2-aminonaphthalene and several terminal-silated alkyne derivatives via palladium-catalyzed cyclization reactions is also reported.

CHAPTER I. INTRODUCTION

I. 1. Amino Acids.

α-Amino acids are the corner stone in all living systems. They are present in a free form and as the repeating units in peptides and proteins. Glycine, the smallest amino acid, consists of an amino group and a carboxylic group attached to a single methylene unit. From a strict point of view, all α-amino acids are derivatives of glycine with different side chains attached to the methylene group. All α-amino acids, with the exception of glycine itself, are optically active. In nature, all α-amino acids are **L** configuration, also referred to as the (*S*)- configuration, except for cysteine and cystine (Figure I.1).

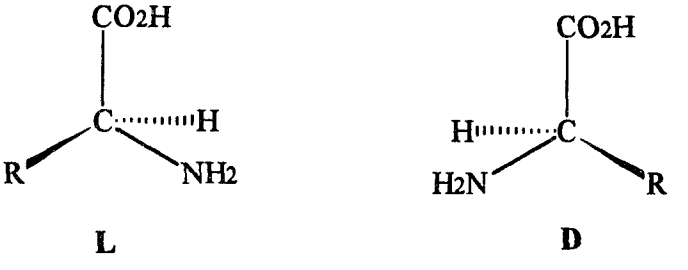


Figure I.1. α-Amino acid configurations

Amino acids possess unique physical and chemical properties: (1) contrary to amines and carboxylic acids, amino acids are nonvolatile crystalline solids which often do not melt, but decompose at high temperatures; (2) they are insoluble in nonpolar solvents such as ligroin, benzene and ethyl ether, but they are somewhat soluble in water; (3) in aqueous solutions, their dipole moments are high; (4) their K_a and K_b values are extremely small. For instance, while glycine has a $K_a = 1.6 \times 10^{-10}$ and a

K_b = 2.5 x 10^{-12} the average K_a and K_b values for a carboxylic acid and an aliphatic amine is ~10^{-5} and ~10^{-4}, respectively. In fact, the acidic and basic groups in glycine are not -COOH and -NH_2 but -NH_3^+ and -COO^-, respectively.

The substituents of α-amino acids provide the unique shapes, sizes, hydrophobicities, charges, chemical reactivities and biological activities. When α-amino acids bind covalently, it is via amide connections, they form peptides and proteins.

I. 2. Peptides.

Depending upon the number of amide links within the molecule, peptides are designated as dipeptides, tripeptides, etc., up to a point until they are called polypeptides. Conventionally, all peptides with a molecular weight up to 10,000 units are considered polypeptides; above this value they are referred to as proteins.

Conventional drawing of peptides have the free amino part (N-terminal) on the far left of the molecule and the amino acid residue containing the free carboxylic part on the far right of the molecule.

X-ray studies on amino acids and dipeptides reveal that the amide group lies in a plane where the atomic distance between the nitrogen and the carbonyl carbon is 1.32 Å. This short distance suggests that this N-C bond has a high double-bond character (~50%). Consequently, the bond angles on the nitrogen atom are very similar to those bonds of a trigonal carbonyl group (Figure I.2).

Peptides play an important role in living systems: *glutathione*, for instance, is a tripeptide present in the majority of living cells; the nonapeptide *oxytocin*, a hormone that resides in the pituitary gland, controls the contractions in the uterus; α-corticotropine, a 39-residue peptide, is an important component of the adrenocorticotropic hormone ACTH.

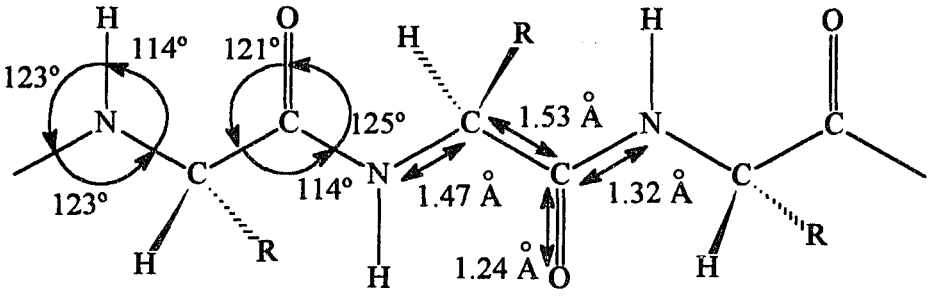


Figure I.2. Bond angles and distances in peptides and proteins

I. 3. Proteins.

A better understanding of peptides will lead to a better comprehension of more complex molecules such as proteins. The word protein comes from the Greek word *proteios* which means "the primary". Certainly, this term describes the meaningful role of such compounds in the complex process of life. Proteins are present in every living cell as major components in skin, muscles, tendons, nerves, blood, enzymes, antibodies, and numerous hormones. There are three types of proteins: 1) fibrous, which are not soluble in water; 2) globular, which are soluble in water, basic and acidic media, and in ionic solutions; and 3) membrane soluble.

Fibrous proteins fold in an organized form due to both electrostatic and Van der Waals interactions to build well defined geometries stabilized by hydrogen bonds, with the α-helix and β-sheet as the most common structural forms. Globular proteins, on the other hand, create clusters with a pseudo spherical shape where the lipophilic parts are inside the cluster and the hydrophilic components are sticking out of the cluster.

Since the solubility and biological activity of proteins and peptides are governed by their intramolecular structural features, it is crucial to understand the relationship between structure and function.

One of the techniques that provides valuable information on peptides and proteins is X-ray diffraction. To date this is the only method that gives precise information about the atomic array in a molecule in the solid state. Unfortunately, peptides and proteins are difficult to crystallize due to the low rotational barrier in the nonamide bonds, less than 3 kcal / mol, which gives the peptide chains high flexibility. However, even when a peptide or a protein crystallizes, it is possible that its molecular structure in solution differs from the one in the solid state.

Another valuable technique is NMR spectroscopy. The principal advantage of this technique is that intramolecular and intermolecular interactions in solution are registered and recorded in the spectrum. However, for proteins and long-flexible peptides the ^{1}H NMR spectra are very complicated to interpret. To overcome some of these limitations, fluorescence spectroscopy is used since it provides dynamic as well as static structural information.

I. 4. Fluorescence.

In general, at room temperature a molecule will be in its ground electronic state. Absorption of the appropriate radiation results in excitation of the molecule into a higher energy level: an excited electronic state.

Fluorescence is the emission of radiation that occurs when a molecule in a singlet excited electronic state returns to the ground state (Figure I.3). This phenomenon lasts for a short period of time, 10^{-8} to 10^{-9} seconds.

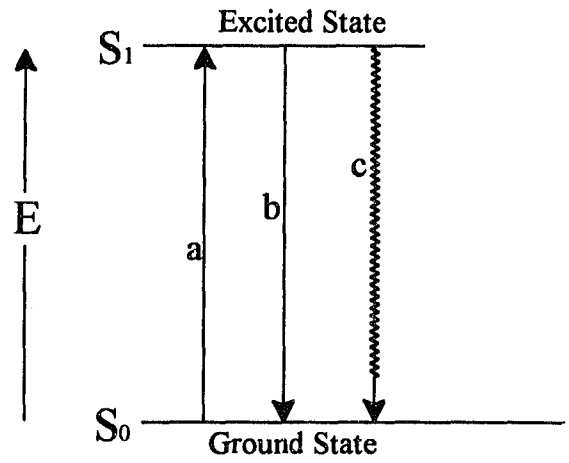


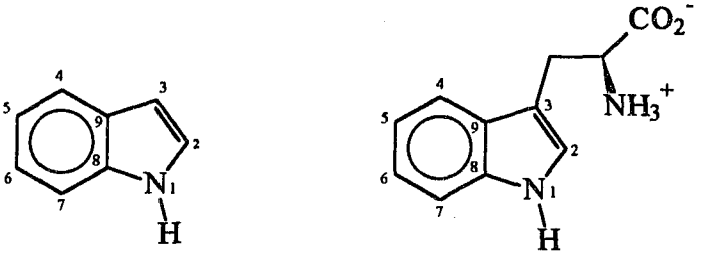
Figure I.3. Simplified Jablonsky diagram

Fluorophores are the molecular groups responsible for fluorescence. Tryptophan (**W**), a naturally occurring amino acid, is a fluorophore widely used as an intrinsic probe of the environments of proteins and amino acids.[1] Absorbance of a photon is due to its chromophore, indole. The term chromophore, which in Greek means "color bringer", is used to describe the unit that gives rise to a selective absorption (Figure I.4).

Unfortunately the complex photophysics of Trp makes it difficult to interpret the fluorescence results. The fluorescence of Trp is complicated in part because indole has two overlapping $\pi \rightarrow \pi^*$ electronic transitions in the first absorption band near 280 nm: ^1L_a and ^1L_b.[2]

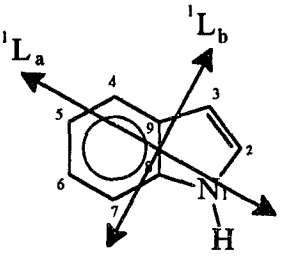
Angular dependency studies on indole as well as fluorescence anisotropy studies of indole in frozen propylene glycol reveal that the ^1L_a and ^1L_b transition moments are approximately at a right angles with respect to one another (-38° and 54° to the long axis

of the molecule, respectively). The ^1L_a transition moment, which has the highest dipole moment, is oriented parallel to the long axis of the molecule (Figure I.5).[3]



Indole Tryptophan (W)

Figure I.4 Indole and Tryptophan



Indole

Figure I.5. ^1L_a and ^1L_b transitions in indole

The ^1L_a transition is broader and absorbs farther to the red than does the ^1L_b transition, the latter having two maxima at 282.5 and 289.5 nm.[4] Absorption at wavelengths longer than 295 nm arises only from the ^1L_a transition.[5]

The fluorescence emission of indole depends greatly on the polarity of the solvent. The ^1L_a transition is much more sensitive to its environment than the ^1L_b transition. The insensitivity of the ^1L_b excited state towards solvent polarity makes this transition higher in energy. In polar solvents the ^1L_a excited state is highly stabilized becoming lower in energy.[6] The observed Stokes shift of the emission in indole is also attributed to relaxation of solvent dipoles about the increased dipole moment of the excited state.[7]

The dynamics of indoles are attributed in part to a coupling interaction between the ^1L_a and ^1L_b states. The controversial ^1L_a state is believed to be coupled to triplet state levels or higher vibrationally excited ground states levels. The ^1L_a state in indole is thought to cause changes in the electron density at the ring nitrogen in the excited state making the N-H group a better proton donor. Cluster formation with proton acceptors confirms that ligand interaction increases the coupling between the ^1L_a and ^1L_b states. However, it is also postulated that clustering with the π-system of indole and its derivatives gives rise to broad, unstructured emission which has been taken as a signature of the ^1L_a state.[8]

Fluorescence excitation spectra of jet-cooled indole-H_2O complexes[9] propose that the less red-shifted complex (^1L_b character) has the water as an H-bond acceptor from the indole H-N while the more red-shifted complex (^1L_a character) has the water acting as a donor in a H-bond to the indole π-system, as recently documented for benzene-water.[10] However, fluorescence excitation spectra of jet-cooled indole-D_2O questions the latter complex.[11]

Subpicosecond fluorescence anisotropy measurements in aqueous solutions show that the interconversion time scale between the ^1L_b and ^1L_a excited states is 1.6 ± 0.2 ps. This interconversion is followed by reorientation of the ^1L_a transition moment whose emission lasts longer than 5 ps.[12] The time scale for the ^1L_a excited state reorientation

at pH 7 is 34.8 ± 1 ps at 20 °C.[13] Molecular dynamics studies on rotational reorientation of Trp in water using standard molecular dynamics packages such as GROMOS (Groningen molecular simulation system) and CHARMm (chemistry at Harvard molecular mechanics) find that the L_a vector reorients faster than the L_b vector which suggests a substantial role for the alanyl side chain in determining the dynamics.[14,15,16,17]

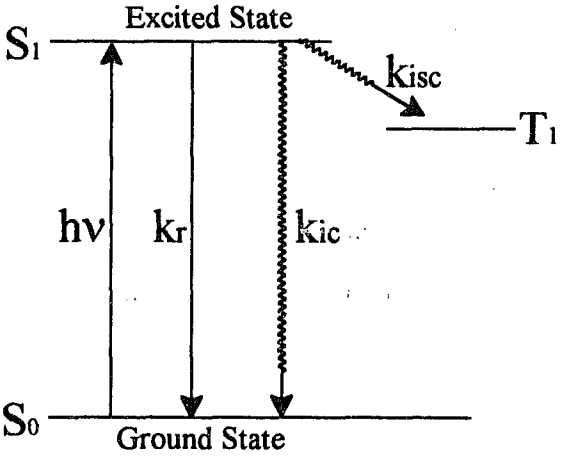
Indole shows a mono-exponential fluorescence decay with a lifetime of 4.8 ns at neutral pH,[21] but this is not the case with Trp. Tryptophan exhibits a double-exponential fluorescence decay where the major component has a lifetime of 3.1 ns with a maximum emission at 350 nm while the minor component has a lifetime of 0.5 ns with a maximum emission at 335 nm.[20] The fluorescence decay of zwitterionic Trp fits well to two exponentially decaying components, namely to the function $K(t) = 0.22 \exp(-t / 620 \text{ ps}) + 0.78 \exp(-t / 3200 \text{ ps})$.[22,5] The simultaneous emission from ^1L_a and ^1L_b excited states had been proposed as one of the explanations for this biexponential fluorescence decay. But this interpretation was eventually discarded by the authors.[18,19,20]

The fluorescence quantum yield of Trp is pH-dependent. At high pH (above 11) the fluorescence quantum yield increases giving a single-exponential decay with a lifetime of ~9 ns. On the other hand, at low pH (below 3) the quantum yield decreases with the 3.1-ns component disappearing.[18] Interestingly, in the zwitterion only the longer lifetime is temperature dependent. At temperatures below 150 K a single-exponential decay with a lifetime of ~5.4 ± 0.1 ns is detected with an emission maximum shifted to the blue (~ 30 nm).[23]

The spectroscopic and photophysical behavior of indole and its derivatives are temperature-dependent. Fluorescence quantum yields and lifetimes as well as several

nonradiative processes such as photoionization,[24] excited-proton[25] and electron transfer[26,27] are influenced by temperature. Intersystem crossing is probably the only nonraditative temperature-independent deactivating process involved in indole's photophysics.[28]

In fact, the complex photophysics of the zwitterion Trp is due to a combination of nonradiative pathways such as internal conversion, intersystem crossing, excited-state proton transfer, excited-state electron transfer, and solvent isotope effects (Figure I.6).



$$\tau^{-1} = k_r + k_{nr}$$
$$k_{nr} = k_{ic} + k_{isc} + k_{si} + k_{H(D)} + k_{et}$$

Figure I.6. Jablonsky diagram

Internal conversion is a nonradiative pathway where a molecule in its lowest excited energy level loses energy by either emission of heat or intramolecular vibrational and rotational motions to return to its ground electronic state. To date there is no evidence for internal conversion in indoles.

Intersystem crossing is a forbidden process in which a molecule in its lowest excited singlet energy level, where the electrons have their spins paired, falls into a "forbidden" state where the electrons have their spins unpaired, the triplet state. Trp in proteins and some Trp derivatives appear to have two triplet states which suggests that intersystem crossing may depend on both environment and temperature.[24]

Excited-state proton transfer involves two processes: deuterium isotope effect and H-D exchange of aromatic protons. In this nonradiative quenching pathway both fluorescence quantum yield and lifetime increase in D_2O (compared to H_2O) because deuteron transfer is slower than proton transfer.[29,25] A photochemical reaction of Trp in unbuffered D_2O (pD 5.5) monitored by ^1H NMR shows that incorporation of deuterium took place mainly at position C-4 based on the disappearance of the C-4 H doublet at 7.75 ppm. It was also determined that minor deuteration took place at the C-2 and C-7 positions. The quantum yield (ϕ) of the incorporation of deuterium is 0.14 ± 0.02. When the same photochemical reaction is carried out in presence of saturating concentrations of N_2O in D_2O the quantum yield remained constant eliminating photoionization of Trp to hydrated electrons and $Trp^{+\cdot}$ as a possible means for the photosubstitution. Irradiation of Trp-*4*-d_1 (C-4 deuterated) in light water (pH 7.0) results in solvent deuteron-proton exchange to afford Trp ($\phi = 0.09 \pm 0.02$).[30]

Excited-state proton transfer is both temperature and pH dependent. At pH 10.5 the amino group of Trp is unprotonated and the quantum yield is higher ($\phi = 0.31$). The high regioselective incorporation of deuterium into the C-4 position suggests that the α-ammonium group is involved in the photosubstitution. In the proposed mechanism for proton transfer, rotation of both C_α-C_β and C_β-C_γ bonds of the alanyl side chain places the ammonium group close to the C-4 position of the indole moiety to form a seven-membered ring catalyzing the electrophilic protonation reaction in the excited state

(Figure I.7). Further experiments indicate that the N-H proton is not involved in the proton-deuteron exchange reaction.[30,19]

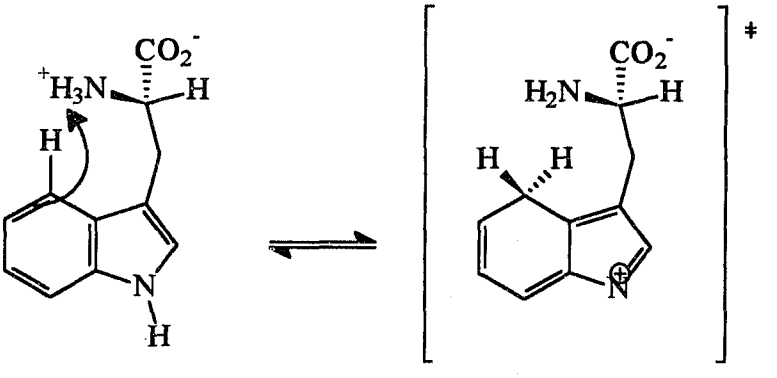


Figure I.7. Saito's mechanism for intramolecular proton transfer

INDO calculations, using the SCF method, predict the following LUMO coefficients for the indole nuclei: C-2 (0.414), C-4 (0.502), and C-7 (0.458). However, the Corey-Pauling-Kolton molecular model (CPK) suggests that only the C-4 position can interact with the ammonium group in the excited state upon rotation of the side chain.[31,19]

Photochemical isotope exchange experiments using glycine-d_5 demonstrate that excited-state proton transfer can also occur via an intermolecular process. N,N,N-trimethylglycine does not quench indole fluorescence showing that the ammonium is essential for quenching.[29]

Excited-state electron transfer is another quenching process believed to occur in Trp. Although both the carboxylate and the ammonium groups were proposed to be electron acceptors, the former is a rather poor intermolecular quencher. However, further studies suggest that its electron acceptor ability is enhanced by the presence of an

adjacent ammonium group.[32,33] On the other hand, the ammonium group is a better intermolecular quencher whose fluorescence quenching rate increases with its acidity.[29]

Initially, it was suggested that fluorescence of Trp could be quenched via intramolecular electron transfer from the indole ring to an electron acceptor group on the amino acid chain.[34,35,22] However, recent studies demonstrate that the ester group shortens fluorescence lifetimes due to an intramolecular through-space excited-state electron transfer process.[36,33] As in excited-state proton transfer, it is proposed that the ethyl ester group must be near the excited indole ring for the electron transfer to occur.[33]

Solvent isotope effects is an excited-state hydrogen-solvent-bonding deactivating processes present in indole's photophysics. In most indoles the quantum yield stays constant from pH 3 to 11; however, at lower and higher pH values the quantum yield falls off rapidly. Trp, on the other hand, has a pH-dependent quantum yield profile. Its quantum yield remains constant from pH 4 to 8.5 (ϕ = 0.14), it rises until pH 10.5 (ϕ = 0.31) and then it drops. Since there is no obvious proton transfer reaction in simple indoles, the intrinsic isotope effect is attributed to external quenching processes such as photoionization, exciplex formation, and charge transfer.

Photoionization is a temperature-dependent process in which a solvated electron and a solvated cation are formed from the excited indole moiety.[31,34,36] In this process it is suggested that the photoelectron is trapped by a four-water-molecule solvent cage that, after a rapid recombination, returns indole to its ground-state. The optimum cage is proposed to be formed from about four water molecules.[37,5] The photoionization of Trp is known to be very small at pH 5.7 (~0.002)[19,38] Photoionization differs from excited-state electron transfer in that the former does not require an electrophilic group to capture the ejected electron. However, picosecond laser photolysis studies of indole

and Trp in water show that electron ejection and solvation occur prior to formation of the relaxed singlet excited state ruling out photoionization as a deactivating pathway for the lowest excited singlet state. Photoionization from a prefluorescent state does not affect the fluorescence lifetime but lowers the apparent fluorescence quantum yield.[36,39] Recent photoionization studies at "zero time" on Trp, indole and some indole derivatives demonstrate that photoionization is excitation-wavelength dependent. The term "zero time" refers to the population of the excited state that remains after the instantaneous photoionization event. Photoionization studies at "zero time" also suggest that ^1L_a is capable of undergoing photoionization as long as this is coupled to ^1L_b. Consequently, solvation of the ^1L_a state will decrease coupling with the ^1L_b state keeping the ^1L_a state from being a source of solvated electrons.[5]

Exciplex formation[40] is another possible quenching mechanism believed to occur between the excited indole moiety and a polar solvent molecule.[31,36,41] The general term exciplex is defined as a complex of simple integer stoichiometry formed between an electronically excited molecule and one or more non-excited partners. Stabilization in exciplexes is predominately a matter of monopole and dipole electrostatic interactions.[42] There are two sites for exciplex formation in indole and its methyl substituted derivatives, N-H and C-3. Initially, it was proposed that C-3 was the electron-rich site capable of interacting even with weak electrophilic reagents, while N-H was the electron-deficient site capable of interacting with bases to form nonfluorescent exciplexes.[43] However, experimentally-correlated semiempirical molecular orbital calculations have predicted that the electron-density rich site is the N-H.[44,11,45,15]

Charge transfer is thought to be an intramolecular nonradiative process interaction between the excited indole (electron donor) and a charged proton donor

(ammonium group, electron acceptor) to stabilize an intramolecular charge-transfer complex.[19,29,23]

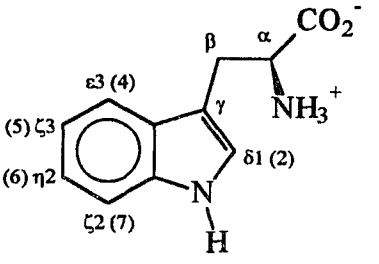
In addition to the various nonradiative pathways of Trp, the rotational degrees of freedom about the C_α-C_β and C_β-C_γ bonds of the alanyl side chain in the ground state complicate the fluorescence decay even more.

Time-resolved spectroscopy of Trp in a supersonic jet confirms the existence of several Trp conformers in the gas phase. All the conformer decays fit well to a single exponential (one lifetime); however, all the lifetimes are not the same.[35,22] While in the gas phase the two lifetimes observed are 10.4 and 12.9 ns, in solution (pH = 7) they are 3.1 and 0.5 ns.[34,46]

Conformational analysis of Trp in solution was carried out using three nuclear magnetic resonance methods. The first method involves the measurement of coupling constants as functions of the dihedral angles (the Karplus equation).[47] The second method involves the assessment of the relative interproton distances using nuclear Overhauser effect. The third method consists in binding a paramagnetic lanthanide ion to the carboxylate group to monitor both shift and relaxation changes to the spectrum in terms of vectors between the different protons and the bound metal ion.

The conformation of Trp is defined by the torsional angles between the C_α-C_β and C_β-C_γ bonds (Figure I.8); however, the coupling constants between the H^α and H^β protons, $J_{\alpha\text{-}\beta 1}$ and $J_{\alpha\text{-}\beta 2}$, depend strongly on the C_α-C_β dihedral angle.

These ^1H NMR studies have been analyzed assuming the existence of six conformers of Trp in solution, three C_α-C_β bond conformers and two C_β-C_γ bond conformers. The three C_α-C_β bond conformers are designated as the g^+, g^- and *t* conformers.[48,49]



Tryptophan (W)

Figure I.8. Nomenclature for tryptophan's carbons and hydrogens

The g^+ conformer has a χ_1 dihedral angle (N-C_α-C_β-C_γ) defined to be 62.7°, as found in the crystal structure;[50] the g^- and *t* conformers have χ_1 values of -57.3° and -177.3°, respectively. The indole part, which is defined by the χ_2 dihedral angle (C_α-C_β-C_γ-$C_{\delta 1}$), is 80% populated with a perpendicular (χ_2 ca. 90°) orientation and 20% populated as an antiperpendicular (χ_2 ca. -90°) orientation (Figure I.9).

The g^- conformer, whose carboxylate group is anti to the indole moiety, is the predominant conformer with a population ranging between 53 and 75%. The remainder of the population is complemented by the g^+ and *t* conformers.[51,52]

These results evoked a lot of controversy in explaining the origin of the two lifetimes of Trp in solution. One theory attributes lifetime heterogeneity to C_α-C_β conformers (χ_1 rotation). However, molecular dynamics simulations, predicting a fast interconversion of the C_α-C_β conformers, supports a second theory that ascribes lifetime heterogeneity to C_β-C_γ conformers (χ_2 rotation).

In addition to this controversy, the fact that six rotamers give rise to only two lifetimes implies that some rotamers must have similar lifetimes, interconvert at the same fluorescence time scale, or they just cannot be resolved.

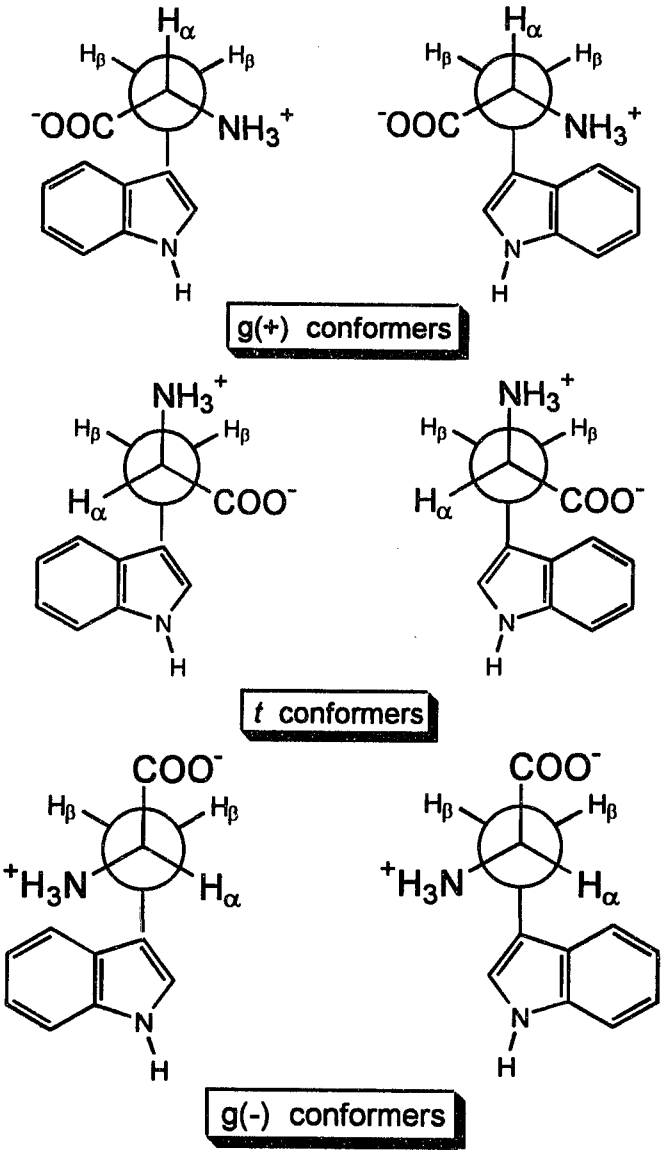


Figure I.9. Trp conformers

I. 5. Fluorescence of Constrained Tryptophan Derivatives.

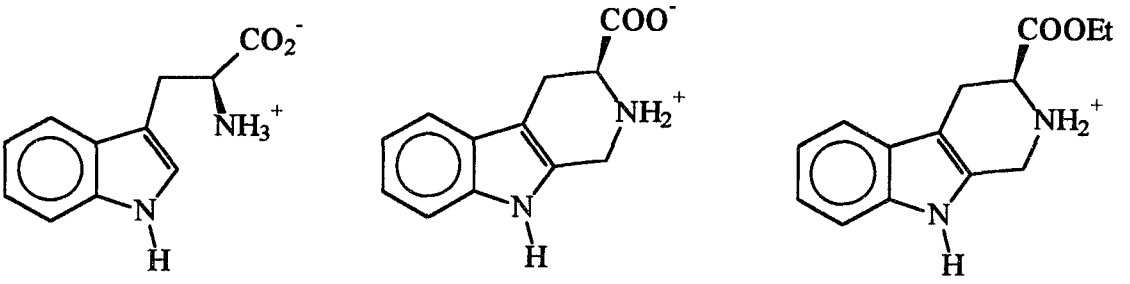
In order to simplify the fluorescence of Trp in solution, constrained Trp derivatives are being synthesized to determine if a one-to-one relationship between fluorescence lifetime and ground-state structure is valid. To determine ground-state structure three powerful techniques are utilized: single crystal X-ray diffraction, molecular mechanics calculations (MM2),[53] and ^{1}H NMR.

Single crystal X-ray diffraction shows the atomic array in a molecule providing valuable information such as solid-state conformation and dihedral angles. The problems with this technique are that the compound of interest must be in a crystalline form, a crystal structure does not rule out the possibility of other conformers in solution, and packing forces might distort the molecule from the most populated conformer in solution.

Molecular mechanics calculations (MM2)[53] are reliable methods to model small molecules. This method also provides valuable information such as enthalpy of formation, rotational barriers, population of conformers, and dihedral angles. The only drawback of this technique is that all the results are purely theoretical.

^{1}H NMR, on the other hand, gives experimental values of molecules in solution. The measurement of coupling constants and the use of a modified version of the Karplus equation,[54] which invokes a linear free energy effect of substituents on coupling constants, can be used to determine the structure of the most populated rotamer in solution as well as rotamer populations.

The synthesis of conformationally constrained Trp derivatives reduces the number of populated rotamers. To date, the most studied constrained Trp derivative is W(1), 3-carboxy-1,2,3,4-tetrahydro-2-carboline, and its ethyl ester derivative W(1)E whose rotation about the C_α-C_β and C_β-C_γ bonds are restricted[18,33,36,55] (Figure I.10).



Tryptophan (W) W(1) W(1)E

Figure I.10. Tryptophan and its constrained derivatives

X-ray diffraction shows that W(1) crystallized in its zwitterionic form having the carboxylate group in a pseudoequatorial position (Figure I.11).[33]

Molecular mechanics calculations (MM2)[53] find only two minimum enthalpy structures as well-characterized half-chair forms of cyclohexene, the T and T' conformers.[56] Except for rotation of the carboxylate group, which differs from the W(1) crystal structure by ~45°, the T conformer correspond to the crystal structure[33] (Figure I.12).

Although the enthalpy difference between the T and T' conformers is ~0.5 kcal/mol, the torsional barrier is $\Delta H^{\ddagger}$ = 5.91 kcal/mol. The T conformer is the one with the lowest enthalpy with a calculated population of 69% (31% for T').

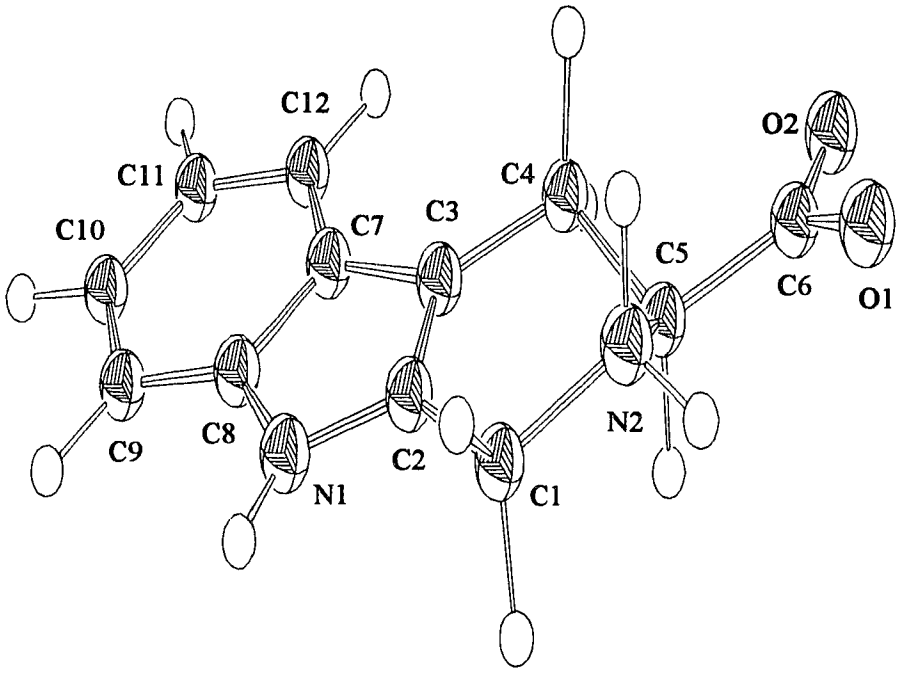
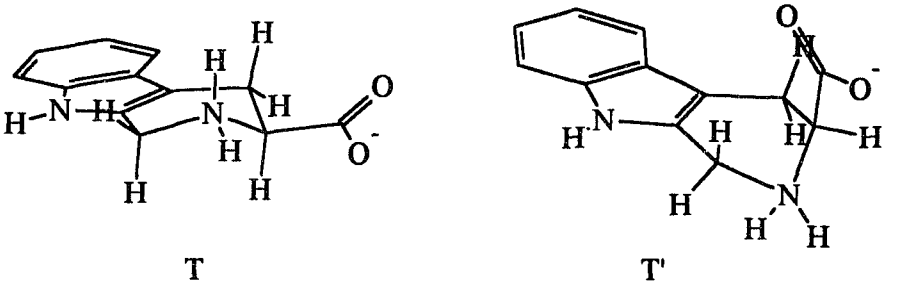


Figure I.11. ORTEP drawing of W(1) zwitterion



T T'

Figure I.12. Half-chair conformers of W(1), T and T'

^{1}H NMR provides the coupling constants between the H_α and H_β protons. Because the dihedral angle N-C_α-C_β-C_γ for the T conformer in the X-ray and MM2 structures is almost identical, -47.3° and -48° respectively, this value was set to -48°. Solving the modified Karplus equation[54] using the measured coupling constants and the fixed dihedral angle, it is determined that the T conformer is 73% populated. This result not only agrees with the MM2 calculated population of the T conformer (69%), but also demonstrates that semiempirical calculations using the MM2 force field combined with X-ray data can provide reliable results.[33] Independently, Durocher and co-workers have also reported the use of X-ray data and semiempirical calculations in photophysic studies of indole derivatives.[57,58,59]

Time-resolved fluorescence on W(1) detects two lifetimes, 6.3 and 3.6 ns. The longest lifetime, 6.3 ns, is assigned to the T conformer (pseudoequatorial carboxylate), and the shortest to the T' conformer (pseudoaxial carboxylate).

W(1)E shows that no excited-state proton transfer reaction takes place at the C12 position (equivalent to C4 in indole) supporting the proposed mechanism for this quenching process.

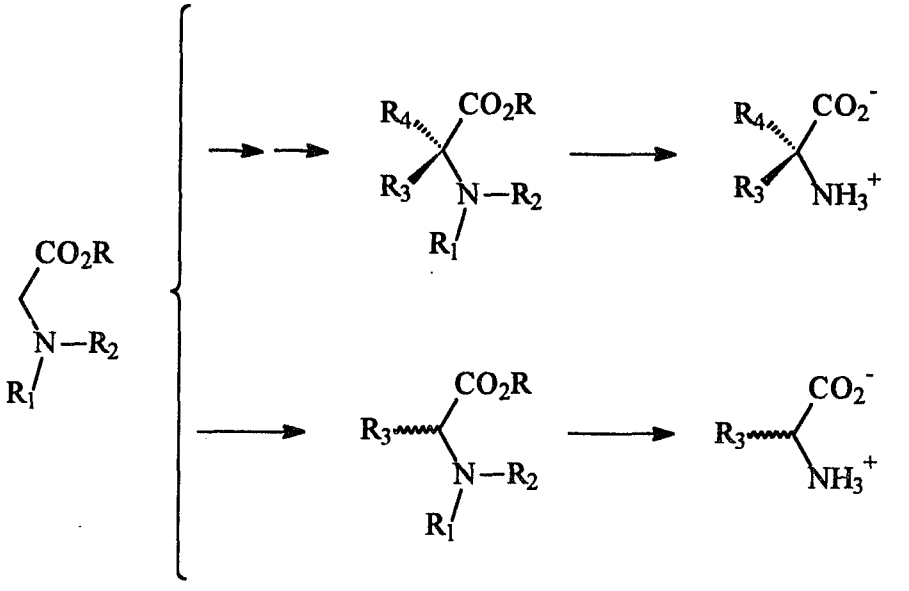
In summary, by limiting the rotational freedom of the alanyl chain in W(1) and W(1)E it is demonstrated that (1) ground-state rotamers that do not interconvert on the fluorescence time scale can account for the complex decay of Trp, (2) the nonradiative pathway excited-state proton transfer is suppressed, (3) substitution of carboxylate by ethyl ester, a more electrophilic group[27] shortens the fluorescence lifetimes, 5.0 and 2.4 ns, suggesting quenching via intramolecular through-space electron transfer is extant.

However, W(1) and W(1)E differ from Trp in having both a conformationally restricted framework and an additional methylene group as part of the heterocyclohexene ring. Although it is expected that this methylene unit would not influence the complexity of the photophysics of the fluorescence decay, it is expected to perturb the electronic states.

The goals of this research are: (1) the synthesis of stereochemically constrained Trp derivatives to limit the rotational freedom of the alanyl chain mimicking at the same time the naturally occurring amino acid Trp in a biological context, (2) the synthesis of constrained Aib derivatives for their incorporation into peptides to enhance α-helicity, and (3) the synthesis of benz[*f*]tryptophan to eliminate spectral overlap of this fluorescence probe with other aromatic amino acids in the sample and reduce the number of nonradiative processes.

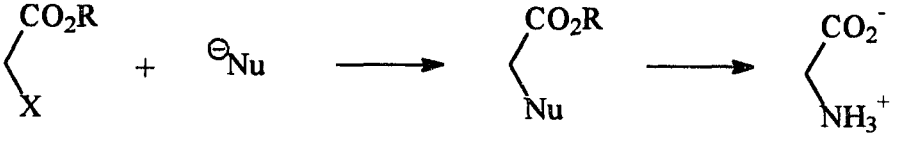
I. 6. α-Amino Acids Synthesis.

Several strategies have been developed to synthesize α-amino acids. (1) Alkylation reactions using glycine derivatives as nucleophiles, Scheme I.1.



Scheme I.1. α-Amino acid alkylation synthesis

(2) Substitution reaction for the incorporation of a precursor to be further transformed into the complementary functional group, Scheme I.2.

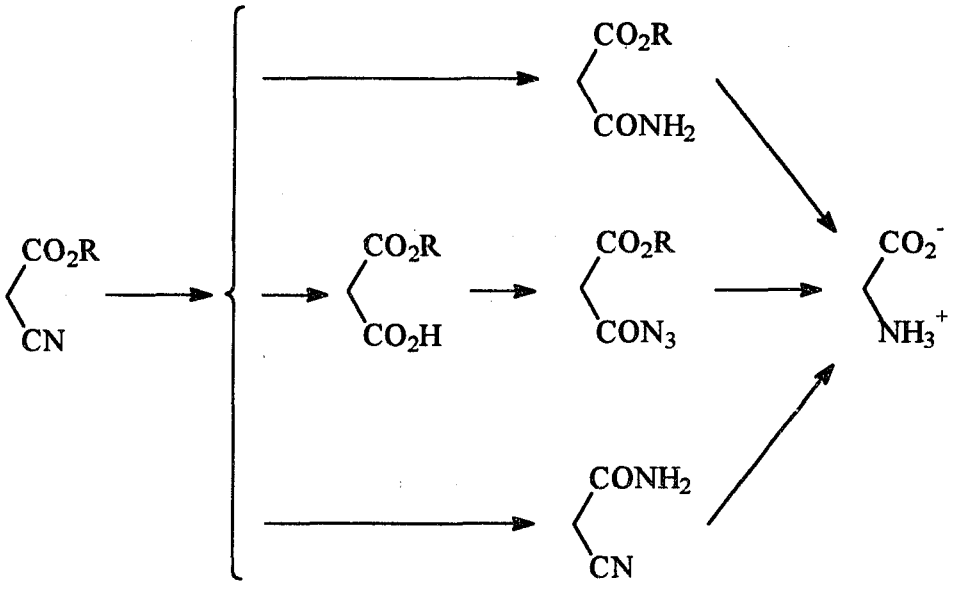


X = Cl, Br, I, OTs

$^{\ominus}$Nu = N_3, NO_2, NHR'

Scheme I.2. α-Amino acid substitution synthesis

(3) Rearrangement reactions such as Curtius, Hofmann, Schmidt, Neber, Stevens, and modified Curtius, Scheme I.3.



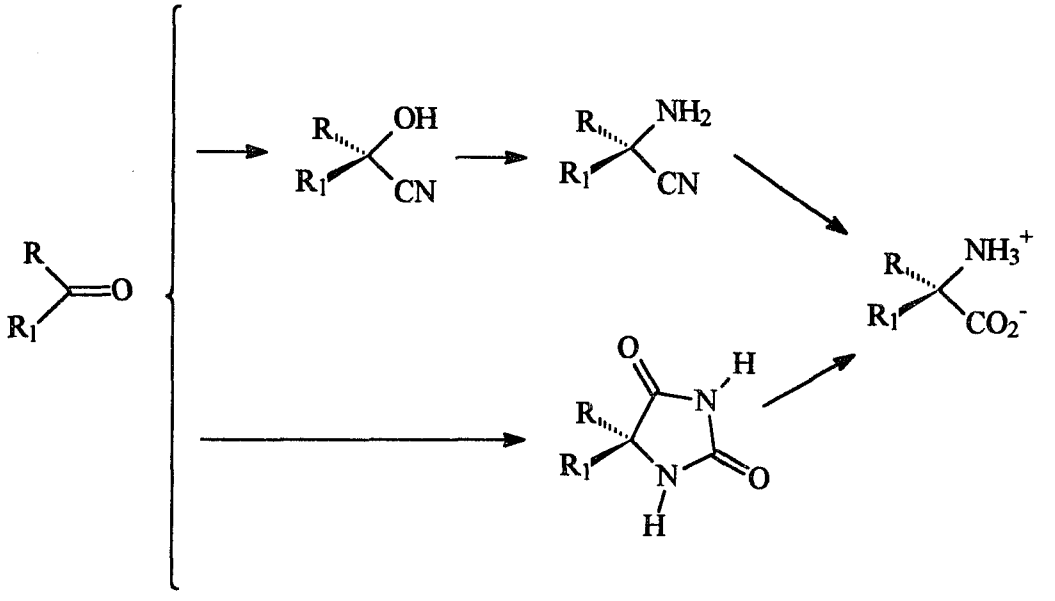
Scheme I.3. α-Amino acid rearrangement synthesis

(4) Condensation reactions including the Strecker synthesis and the Bucherer-Bergs synthesis, Scheme I.4.

The primary disadvantage of these methods is that they provide racemic mixtures. This is a major drawback since the separation of the enantiomers is a tedious and expensive process. To overcome this problem, asymmetric synthesis of amino acids is now the focus of research efforts.

The established methods for the asymmetric synthesis of amino acids can be divided roughly into seven categories. (1) The highly stereoselective hydrogenation of prochiral dehydro amino acid derivatives, (2) chiral glycine equivalents serve as useful α -amino acid templates undergoing homologation via carbon-carbon bond formation at the α-position through nucleophilic carbanion alkylation, (3) electrophilic carbocation substitution, (4) nucleophilic ring-opening on the β-carbon of aziridine-2-carboxylate

derivatives, (5) nucleophilic amination, (6) electrophilic amination of optically active carbonyl derivatives, and (7) enzymatic synthesis.[60,61,62]



Scheme I.4. α-Amino acid condensation synthesis

I.7. Indole Synthesis.

The first synthesis of indole, reported by Baeyer in 1869, involved reductive cyclization of 2-nitrophenylacetic acid followed by zinc-dust pyrolysis. Although at least ten major indole syntheses have been described up to 1984,[63] others have emerged ever since[64]. The most notable methods are: (1) the Fischer indole reaction,[65] (2) the Leimgruber-Batcho synthesis, (3) intramolecular ring closure of *o*-lithiated benzene derivatives,[66,67,68] (4) arynic cyclization of imines or enaminoketones,[69] (5) radical

cyclization of isonitriles,[70] and (6) transition-metal-promoted coupling/cyclization reactions of 2-halo substituted nitro and amino benzene derivatives.

CHAPTER II. RETROSYNTHETIC ANALYSIS

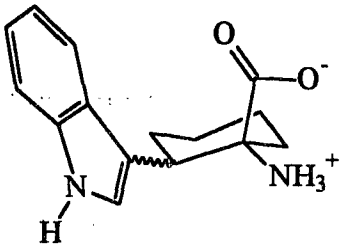
II. 1. Introduction.

Retrosynthetic analysis, also referred to as "antithetic" analysis, is a problem-solving technique in which a target molecule (TG) is dismembered progressively into a sequence of simpler structures that, ultimately, are either commercially available or simple to synthesize.[71]

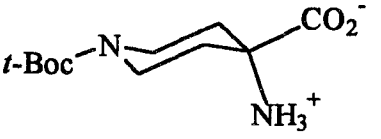
The goal of this research was to synthesize four target molecules. The first target molecule is a constrained Trp derivative whose rotation about the C_α-C_β and C_β-C_γ bonds is restricted by the incorporation of a cyclohexane ring, 1-amino-2-(3-indolyl)cyclohexan-1-carboxylic acid, W(3). The second target molecule is an Aib derivative having an N-protected piperidine framework, 4-amino-N-(*t*-Boc)-piperidine 4-carboxylic acid. The third target molecule is a benzannulated indole analog, benz[*f*]indole. The fourth target molecule is a benzannulated derivative of tryptophan, benz[*f*]tryptophan, Scheme II.1.

II. 2. Target Molecule 1.

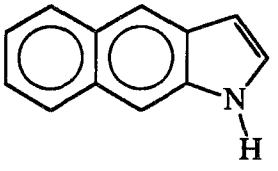
Two possible ways to synthesize 1-amino-2-(3-indolyl)cyclohexan-1-carboxylic acid , W(3), were explored. The first route (pathway A) involves the synthesis of a half-acid half-ester indole intermediate which is expected to afford its corresponding α-amino-protected ester via Curtius rearrangement. The key step in this pathway is the formation of a six-membered ring on a Trp-precursor framework, an indolyl acrylate derivative (dienophile), via Diels-Alder reaction. This indolyl acrylate derivative comes from a condensation reaction between a malonate ester and indole-3-carboxaldehyde, Scheme II.2.



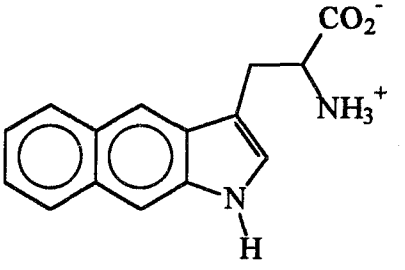
W(3)



4-Amino-N-(t-Boc)-piperidine-4-carboxylic acid



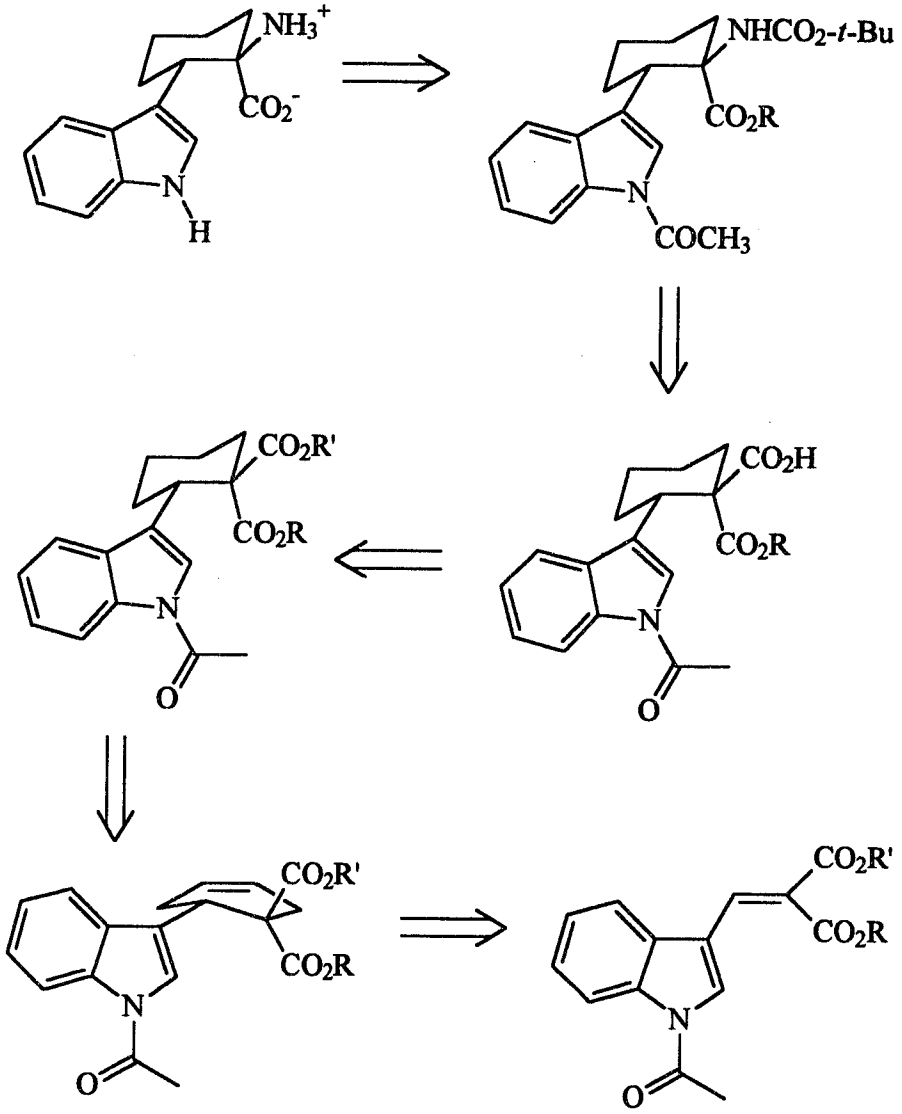
Benz[*f*]indole



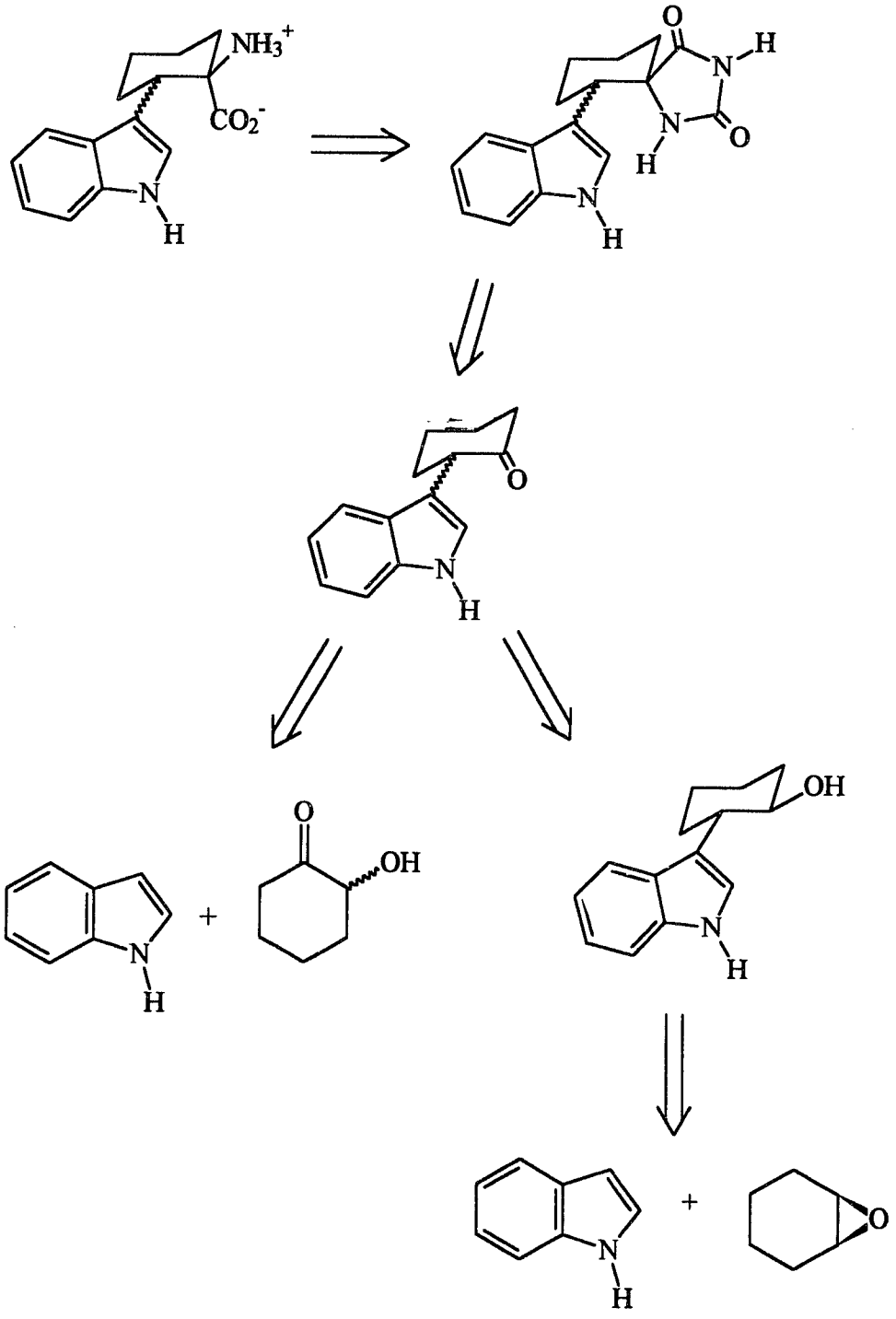
Benz[*f*]tryptophan

Scheme II.1. Target molecules

The second route (pathway B) involves the incorporation of the α-indolyl group in cyclohexanone to afford the desired α-amino acid via Strecker reaction. There are two methods to synthesize 2-(3-indolyl)cyclohexanone. One method handles the addition of indole into cyclohexanone through a Friedel-Crafts-like reaction (pathway B1). The second method affords 2-(3-indolyl)cyclohexanone via oxidation of its corresponding alcohol precursor (pathway B2), Scheme II.3.



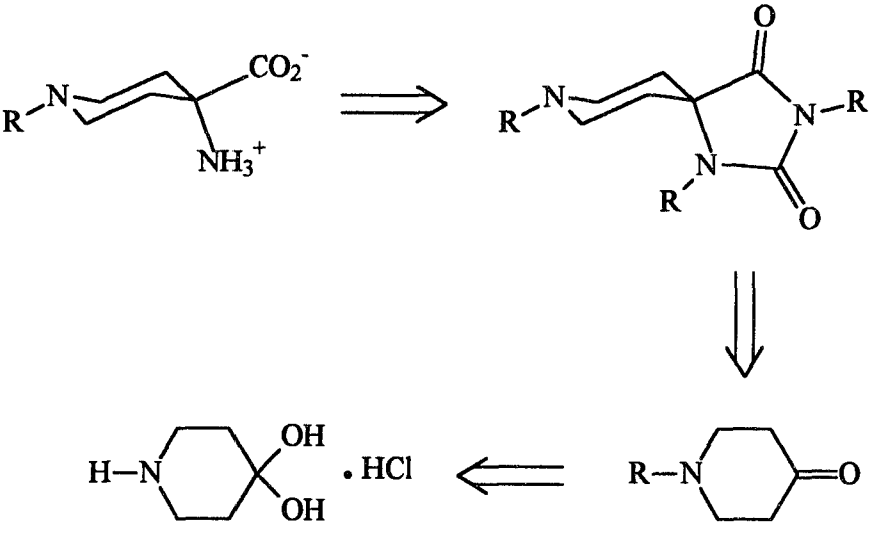
Scheme II.2. Retrosynthetic analysis of W(3) (pathway A)



Scheme II.3. Retrosynthetic analysis of W(3) (pathways B1 and B2)

II. 3. Target Molecule 2.

There are two potential routes for the synthesis of , 4-amino-N-(*t*-Boc)-piperidine 4-carboxylic acid. The first route starts with the synthesis of 4-amino-piperidine-4-carboxylic acid from a piperidine derivative. The piperidine nitrogen of this Aib analog can be eventually *t*-Boc protected under standard conditions. The alternative starts with an N-(*t*-Boc)-protected piperidine derivative to obtain in a straight fashion the N-(*t*-Boc)-protected Aib analog, Scheme II.4.

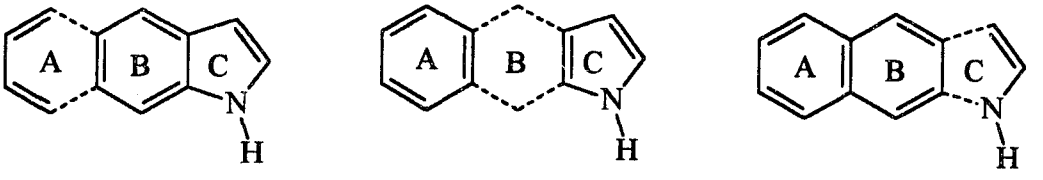


Scheme II.4. Retrosynthetic analysis of 4-amino-N-(*t*-Boc)-piperidine 4-carboxylic acid

II. 4. Target Molecule 3.

There are three suitable approaches for the synthesis of benz[*f*]indole: (i) construction of the A-ring on a BC-ring portion (indole nucleus) (pathway A), (ii)

formation of the B-ring between a phenyl and a pyrrole residue (pathway B), and (iii) construction of the C-ring on an AB-ring moiety (naphthalene derivative) (pathway C), Scheme II.5.



Pathway A Pathway B Pathway C

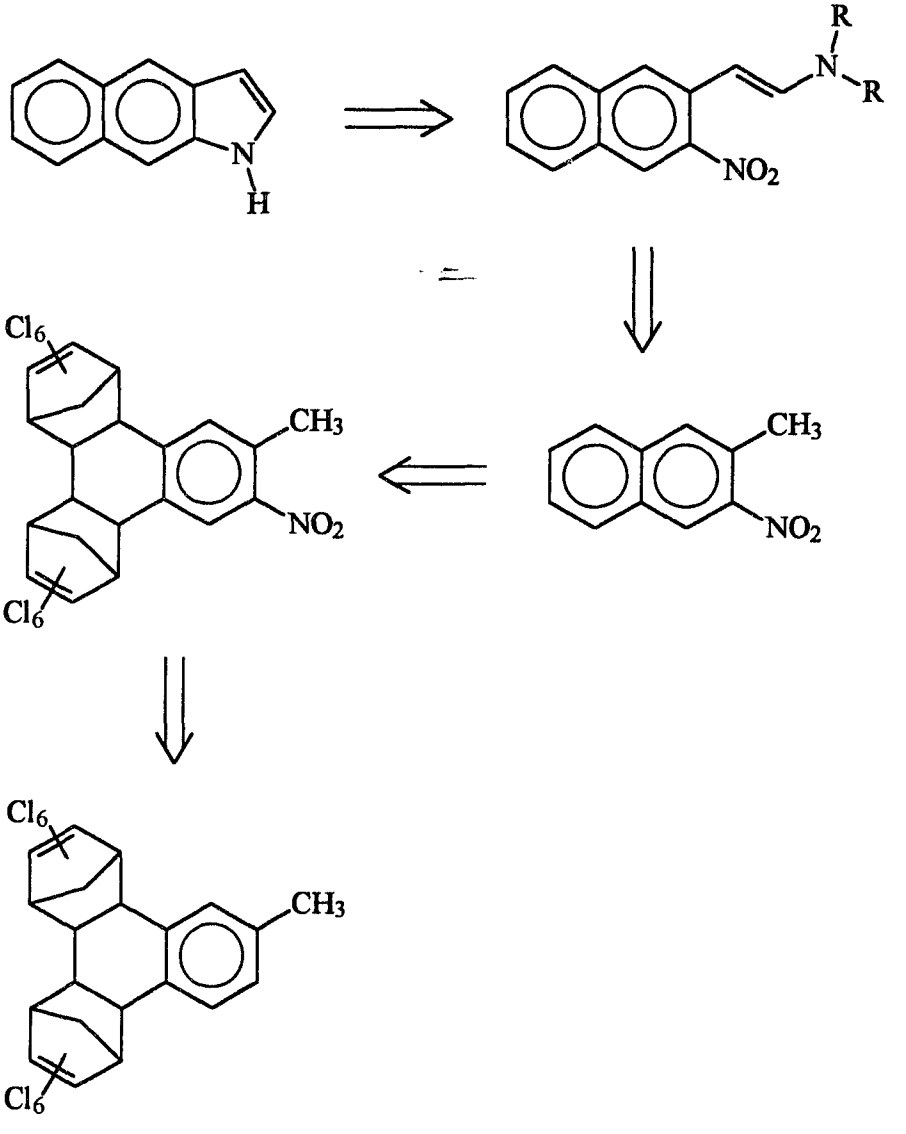
Scheme II.5. Pathways A-C for benz[*f*]indole

Based on the synthesis of indole from 2-nitrotoluene via the Batcho-Leimgruber method,[72] it was decided to explore pathway C. In the same way 2-nitrotoluene can be transformed into indole, it was anticipated that benz[*f*]indole could be synthesized in the same fashion starting from 3-methyl-2-nitronaphthalene. This naphthalene intermediate comes from regioselective nitration of 2-methylnaphthalene which in turn is formed via retro Diels-Alder from its corresponding dicyclohexachlorocyclopentadiene precursor, Scheme II.6.

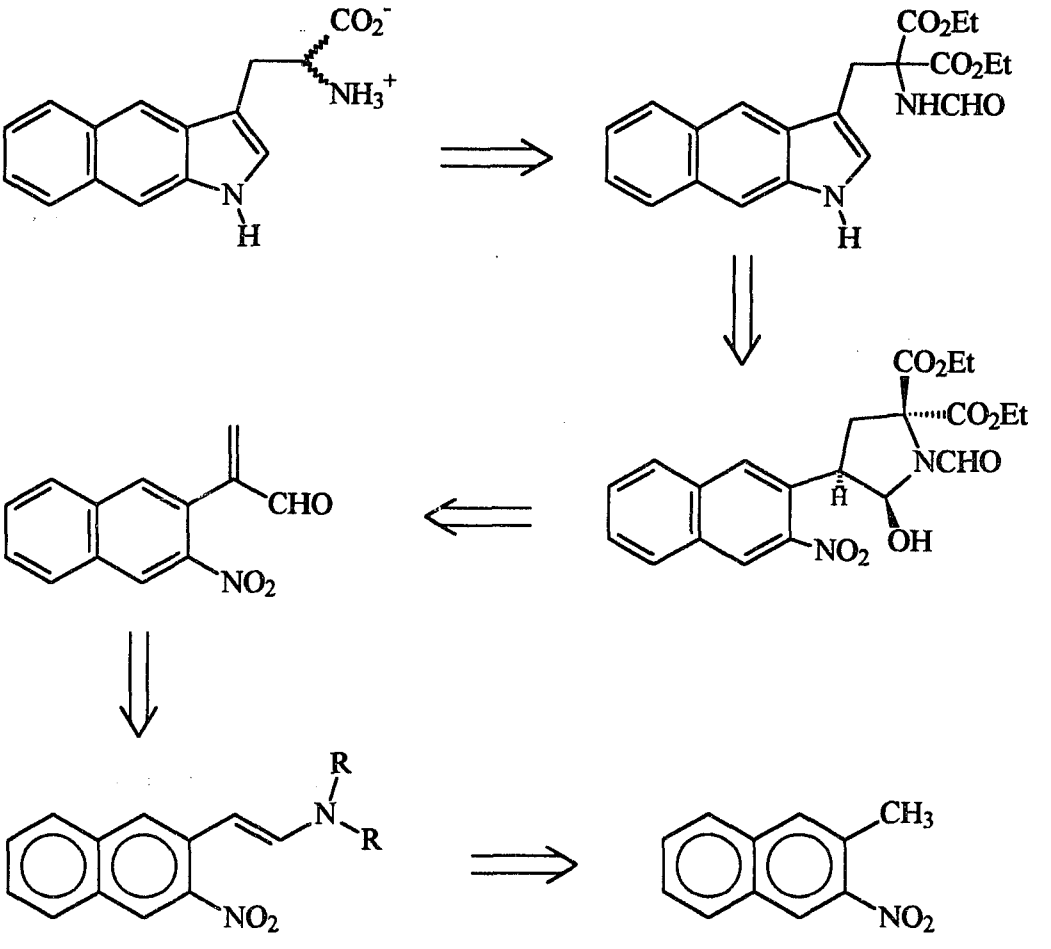
II. 5. Target Molecule 4.

Two synthetic approaches were explored towards the synthesis of benz[*f*]tryptophan. The first approach, pathway A, involves the formation of naphthyl pyrrolidine intermediate which would come from a Michael addition reaction between a glycine precursor (nucleophile) and a naphthyl acrolein derivative.[72] This napththyl

acrolein derivative could be made using previously made 3-methyl-2-nitronaphthalene, Scheme II.7.



Scheme II.6. Retrosynthetic analysis of benz[*f*]indole (pathway C)



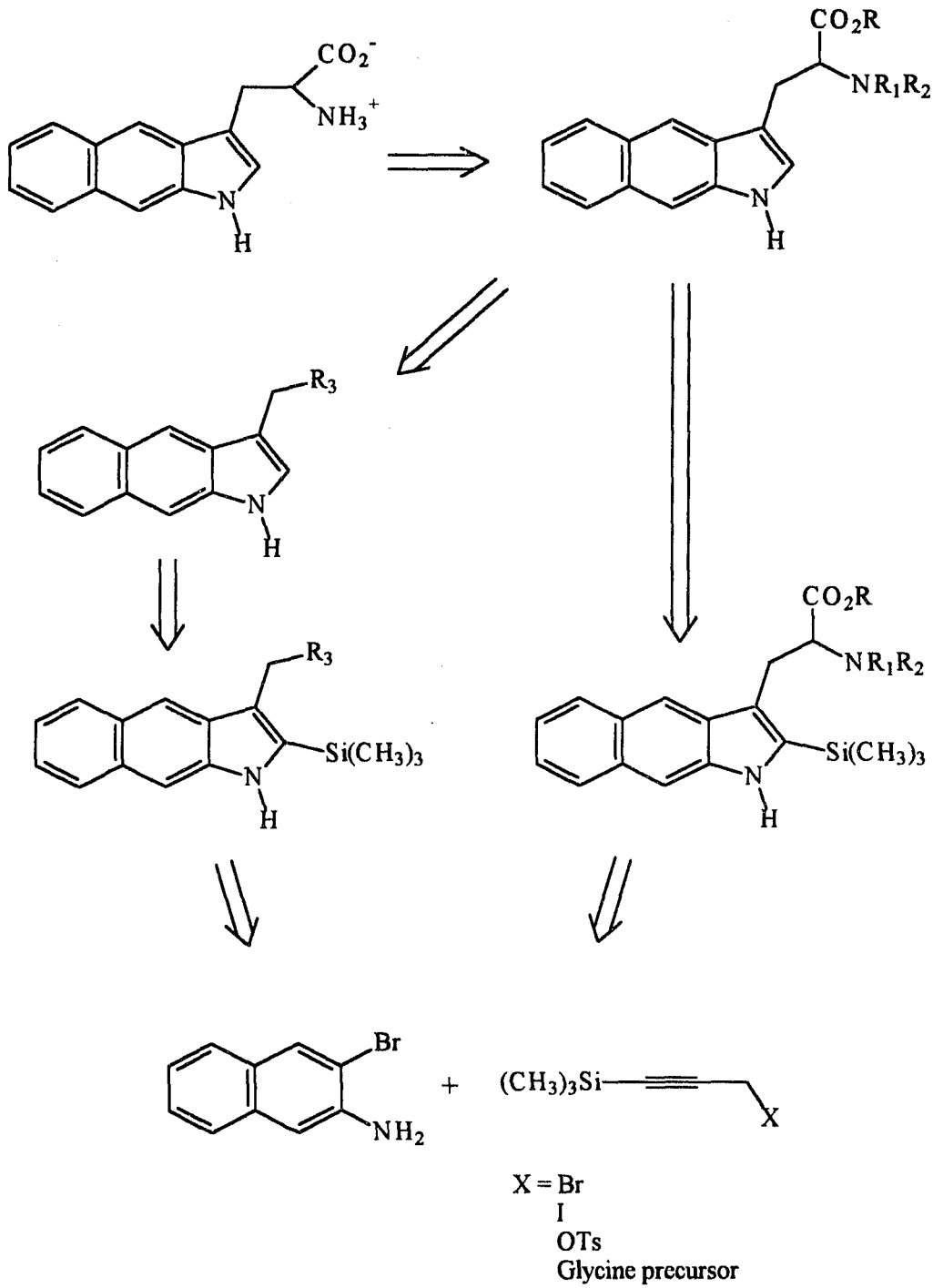
Scheme II.7. Retrosynthetic analysis of benz[*f*]tryptophan (pathway A).

The second approach, pathway B, deals with the formation of the benz[*f*]indole framework through a palladium-catalyzed reaction using a 3-halo-2-amine naphthyl derivative and a terminal-silylated propargyl intermediate ($Me_3SiC{\equiv}C\text{-}CH_2$- unit). There are two ways to use the propargyl unit. One route involves a terminal-silated propargyl unit bearing a good leaving group (-Br, -I, tosylate) to afford a 3-methyl-benz[*f*]indole derivative with a good leaving group attached to the 3-methyl unit. Such good leaving

group could facilitate the asymmetrical incorporation of a chiral or prochiral glycine template into the benz[*f*]indole framework.[73,74,60,75]

The alternative route involves a glycine-precursor-containing propargyl system which, after undergoing palladium-catalyzed cyclization, would be expected to provide the benz[*f*]tryptophan framework.

These palladium-catalyzed cyclization reactions are expected to form 3-methyl-substituted 2-trimethylsilylbenz[*f*]indole derivatives which, after desilylation, would provide the expected target molecules, Scheme II.8.



Scheme II.8. Retrosynthetic analysis of benz[*f*]tryptophan (pathway B).

CHAPTER III. RESULTS AND DISCUSSION

III. 1. SYNTHESIS OF CONSTRAINED AMINO ACIDS.

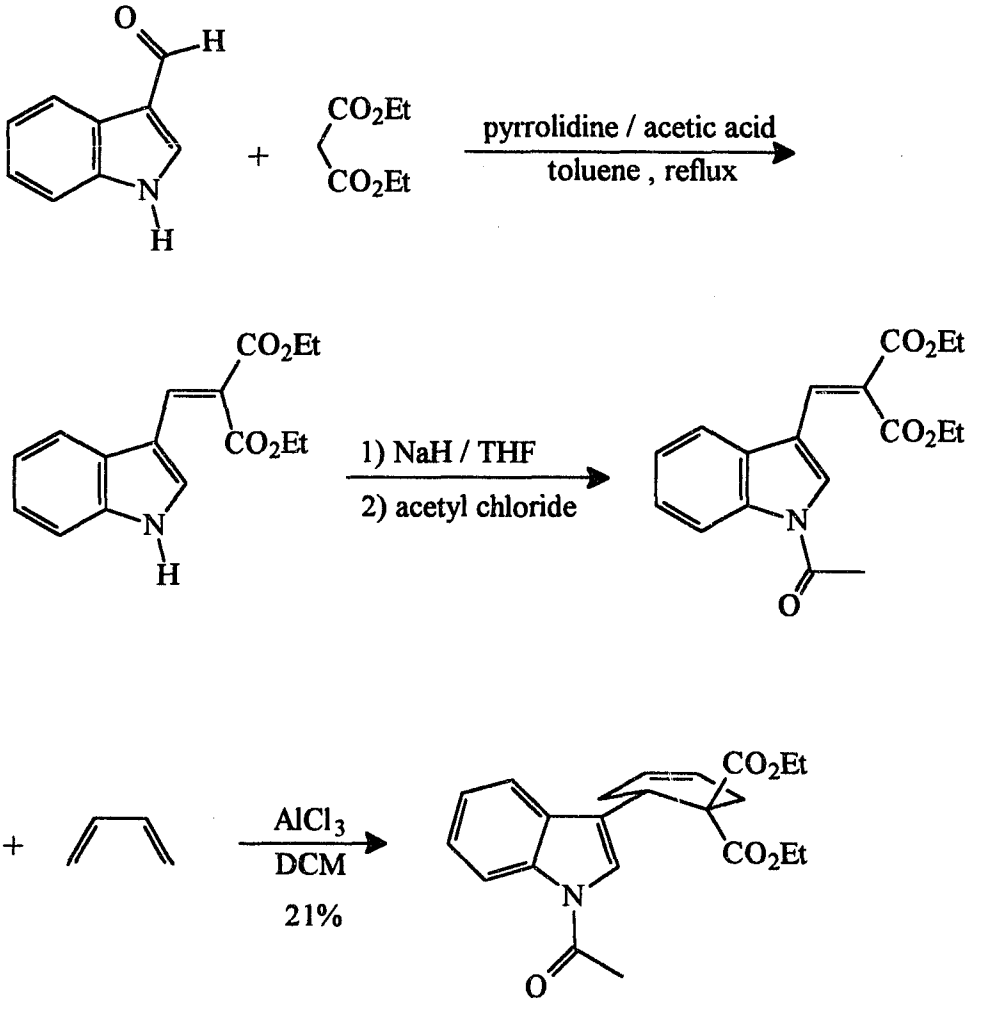
III.1.1 A Constrained Tryptophan Derivative.

Diels-Alder reactions of 2- and 3-vinyl-indoles are well known to produce [*a*] and [*b*]annelated indole and carbazoles.[76,77,78] In fact, Diels-Alder reactions are difficult to occur exclusively on the exocyclic vinyl unit of 2- and 3-vinyl-indoles. Pindur and Pfeuffer achieved, for the first time, a selective [4+2] cycloaddition on the vinyl unit via inverse-electron-demand Diels-Alder reaction.[79] Recently, Bruncko and Crich synthesized an unsaturated constrained indole derivative from a Trp analog. This unsaturated constrained indole derivative is reported to undergo Diels-Alder with cyclopentadiene providing its corresponding Diels-Alder adduct in good yields.[80] However, to date, no successful Diels-Alder cycloaddition reaction between 2- and 3-vinyl-indoles and butadiene has been documented.

In order to synthesize 1-amino-2-(3-indolyl)cyclohexan-1-carboxylic acid, a constrained Trp analog, two synthetic approaches were explored. The first approach consisted of building the cyclohexane framework via a Diels-Alder reaction between butadiene and ethyl 2-carboethoxy-3-(N-acetyl-3-indolyl)acrylate in presence of a Lewis acid, Scheme III.1.

Ethyl 2-carboethoxy-3-(3-indolyl)acrylate was made by refluxing commercially available indole-3-carboxaldehyde and diethyl malonate in toluene with catalytic amounts of pyrrolidine and glacial acetic acid followed by azeotropic water-removal. The workup of the final reaction mixture gave a solid which upon recrystallization in hot ethanol afforded yellow crystals in a 53% yield, mp = 90-92 °C. The ^{1}H NMR spectrum recorded the indole proton at 9.21 ppm as a broad singlet, the methylene protons as a multiplet at

4.37-4.27 ppm and the methyl protons of the ester moiety as a multiplet at 1.37-1.24 ppm. ^{13}C NMR recorded the two carbonyl carbons at 168.12 and 165.40 ppm.



Scheme III.1. Synthesis of diethyl 6-(N-acetyl-3-indolyl)cyclohex-3-en-1,1-dicarboxylate

Since indole derivatives are known to undergo Diels-Alder acting as diene species, it was necessary to incorporate an electron-withdrawing protecting group on the indole

heteroatom to increase the electron deficiency on the acrylic double bond. Ethyl 2-carboethoxy-3-(3-indolyl)acrylate was treated with NaH in anh. THF at 4 °C followed by acetyl chloride to give ethyl 2-carboethoxy-3-(N-acetyl-3-indolyl)acrylate as a white solid in a 79% yield. GC-MS analysis showed the presence of only one compound with a m/z of 329, which corresponds to the mass of the expected product. The ^{1}H NMR spectrum revealed the disappearance of the indole proton and registered the protons of the acetyl group as a singlet at 2.66 ppm integrating for 3 protons. ^{13}C NMR spectrum recorded three carbonyl units at 168.55, 165.86, and 164.28 ppm.

The Diels-Alder reactions were carried out by bubbling butadiene into the indole/DCM solution at -70 °C in an argon atmosphere in the presence of a Lewis acid. Of the three Lewis acids that were tested, BCl_3, $EtAlCl_2$, and $AlCl_3$, only the latter afforded product as a yellow oil. Purification of the yellow oil by column chromatography over silica gel using a solution of hexanes\ethyl acetate (4:1) gave a yellow oil which after crystallization from hot hexanes afforded diethyl 6-(N-acetyl-3-indolyl)cyclohex-3-en-1,1-dicarboxylate as white crystals in 21% yield, mp = 98-99 °C. GC-MS revealed the presence of only one signal with a m/z of 383, the mass of the expected product. The ^{1}H NMR spectrum recorded the newly-made vinyl protons of the cyclohexene moiety as a singlet at 5.83 integrating for 2 protons. X-ray analysis confirmed that the Diels-Alder reaction took place exclusively on the acrylic double bond as predicted (Figure III.1).

Due to the low yield afforded in the Diels-Alder approach, another synthetic route was explored. The second approach involved two goals: (1) the incorporation of the indole moiety into a cyclohexane derivative, and (2) the incorporation of the indole moiety vicinal to a amino-acid-precursor functional group.

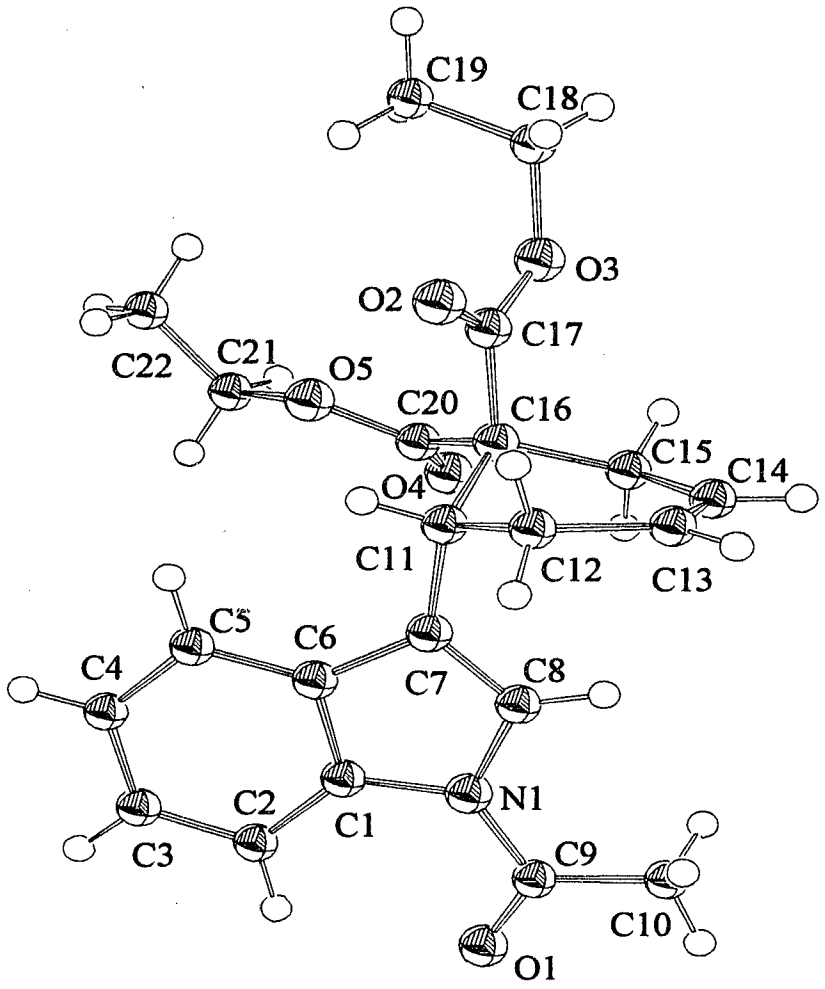


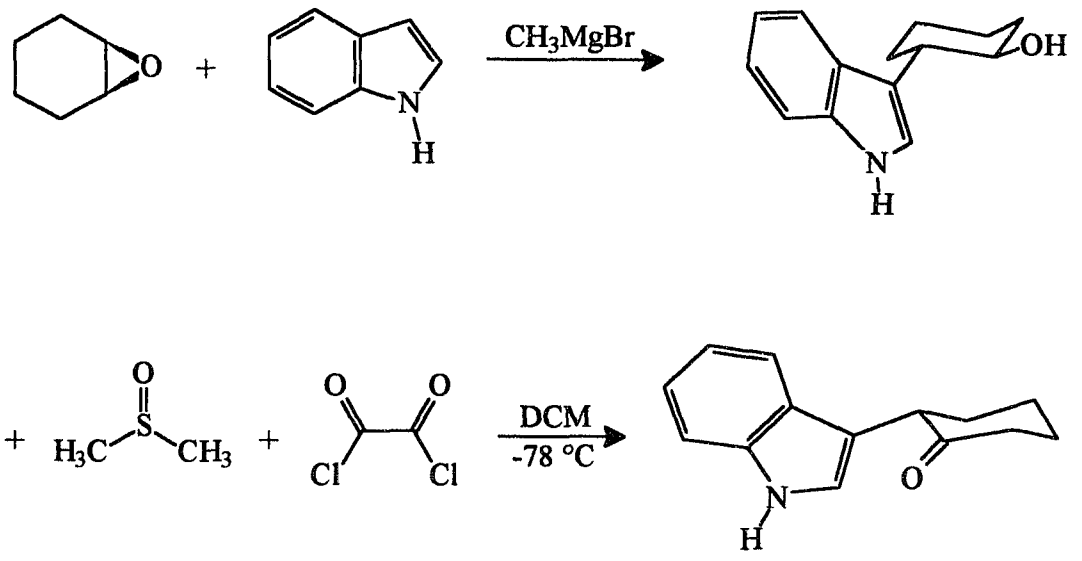
Figure III.1. ORTEP drawing of diethyl 6-(N-acetyl-3-indolyl)cyclohex-3-en-1,1-dicarboxylate

It was decided that 2-(3-indolyl)cyclohexanone would be the perfect candidate for this synthetic approach since the molecule has a cyclohexane framework, has a carbonyl group which could be converted into an α-amino acid via Strecker synthesis, and bears an indolyl group vicinal to the carbonyl group.

There are two synthetic routes reported to synthesize 2-(3-indolyl)cyclohexanone. One route involves the oxidation of its corresponding alcohol precursor, and the other involves the incorporation of the indole moiety into 2-hydroxy-cyclohexanone via Friedel-Crafts reaction.

To explore the first route *trans*-3-(2-hydroxycyclohexyl)indole was synthesized in a 40% yield by reacting indole with methyl magnesium bromide at room temperature followed by cyclohexene oxide. GC-MS analysis showed one signal with a m/z of 215 corresponding to the mass of the expected product. The ^{1}H NMR spectrum recorded the proton on the cyclohexane carbon adjacent to the indole as a multiplet at 2.75 ppm integrating for one proton and the proton on the carbon bearing the hydroxyl group as a triplet of doublets at 3.78 ppm. The large coupling between these two protons, $J = 9.9$ Hz, provides evidence that the molecule obtained was the *trans* isomer.

Attempts to oxidize this alcohol derivative via Swern oxidation, following recently published reaction conditions, failed in providing the desired keto derivative. Several modified Swern oxidations were carried out on the above alcohol; however, only two routes produced the desired ketone in low quantities (5% yield or less). GC-MS analysis revealed the presence of a compound with a m/z of 213, matching the mass of the desired keto derivative. The ^{1}H NMR spectrum showed the disappearance of the proton on the carbon bearing the alcohol substituent (3.78 ppm) and, furthermore, the spectrum was identical to the one published in the literature, Scheme III.2.



Scheme III.2. Synthesis of 2-(3-indolyl)cyclohexanone via Swern oxidation

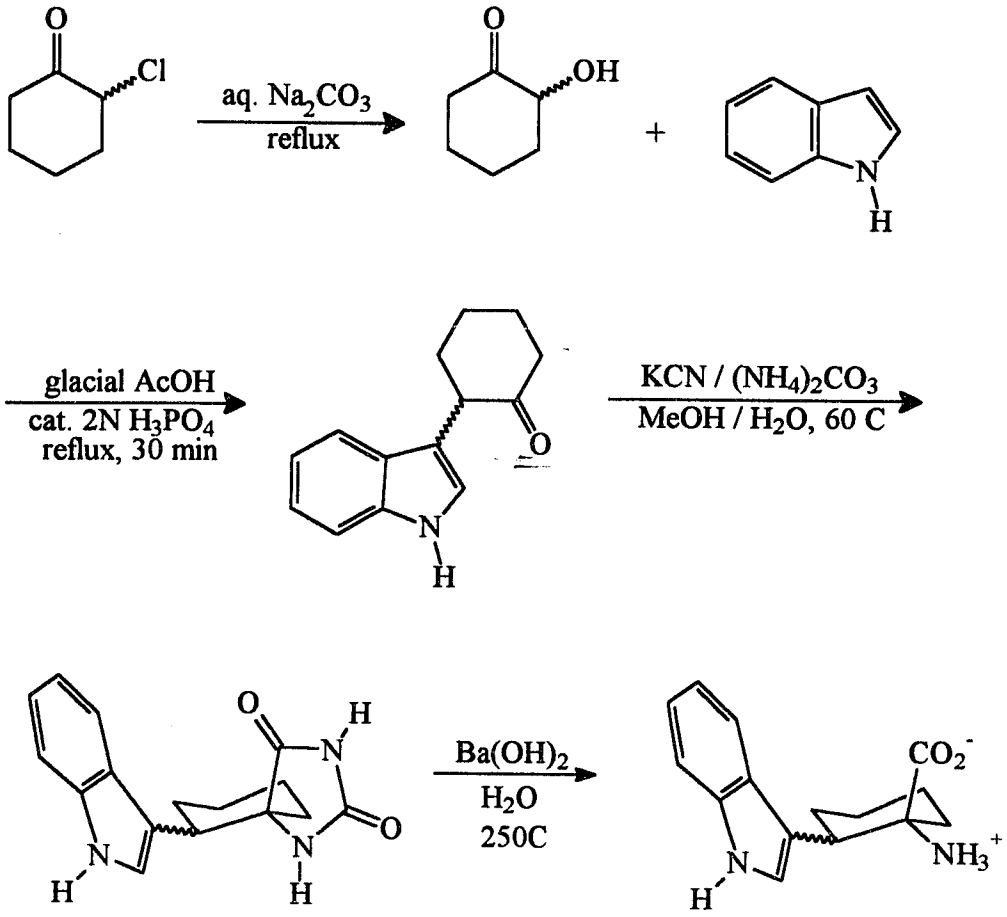
The synthesis of 2-(3-indolyl)cyclohexanone was achieved via a Friedel-Crafts reaction between indole and 2-hydroxy-cyclohexanone. 2-Hydroxy-cyclohexanone was made by refluxing commercially available 2-chlorocyclohexanone in aq. Na_2CO_3 for 1 h. Cooling the resulting light yellow solution for 3 days afforded 2-hydroxy-cyclohexanone (dimer) as a white solid. Crude 2-hydroxy-cyclohexanone and indole were refluxed at 135-140 °C for 30 min in glacial acetic acid using a catalytic amount of 2N H_3PO_4 to give a yellow mixture. The final reaction mixture was cooled by using an ice-water bath and poured carefully under vigorous stirring into conc. aq. NH_4OH to form a yellow solid. The solid was extracted in ethyl acetate, washed with 5% NH_4Cl, dried over anh. $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel using first DCM followed by ethyl acetate to give a light

pink solid in a 30% yield. GC-MS confirmed the solid was the desired alcohol showing a spectrum identical to the one obtained previously (m/z = 213).

This keto-indole derivative was converted into its corresponding hydantoin by reacting it with KCN and $(NH_4)_2CO_3$ in a solution of $MeOH/H_2O$ (1:1) at 60 °C in a 70% yield, Scheme III.3. The ^1H NMR spectrum showed the three different N-H protons as singlets at 10.87, 9.98, and 8.49 ppm integrating for one proton each, and the proton on the cyclohexane carbon adjacent to the indole as a doublet of doublets at 3.26 ppm integrating for one proton. The ^{13}C NMR spectrum recorded the two carbonyl carbons at 177.72 and 156.92 ppm, the indole carbons between 135.33 and 110.98 ppm, and the cyclohexane carbons between 66.11 and 20.71 ppm. To determine which diastereomer had been formed, A or B, both COSY and NOE experiments were carried out.

Taking as point of reference the signal at 3.26 ppm (dd), COSY experiments revealed an interaction between the 3.26 signal and the signals at 1.98-1.78 ppm, which determines that these signals belong to the two protons adjacent to the single proton. NOE experiments showed that the proton at 10.87 ppm interacted mainly with the aromatic protons, which suggests this must be the indole proton; the proton at 9.98 did not interact with any protons at all, which suggests that this proton must be oriented to point away from the cyclohexane system; and the 8.49 proton interacted with the cyclohexane system. The results obtained by X-ray analysis match with the results obtained by NMR experiments (Figure III.2).

Basic hydrolysis of this indole-hydantoin derivative was attempted at different temperatures and reaction conditions. Hydrolysis of the above hydantoin with $Ba(OH)_2$ and deoxygenated water at reflux temperature (1 at.) for 24 h failed in producing the expected constrained Trp derivative.



Scheme III.3. Synthesis of 2-(3-indolyl)cyclohexanespiro-5'-hydantoin

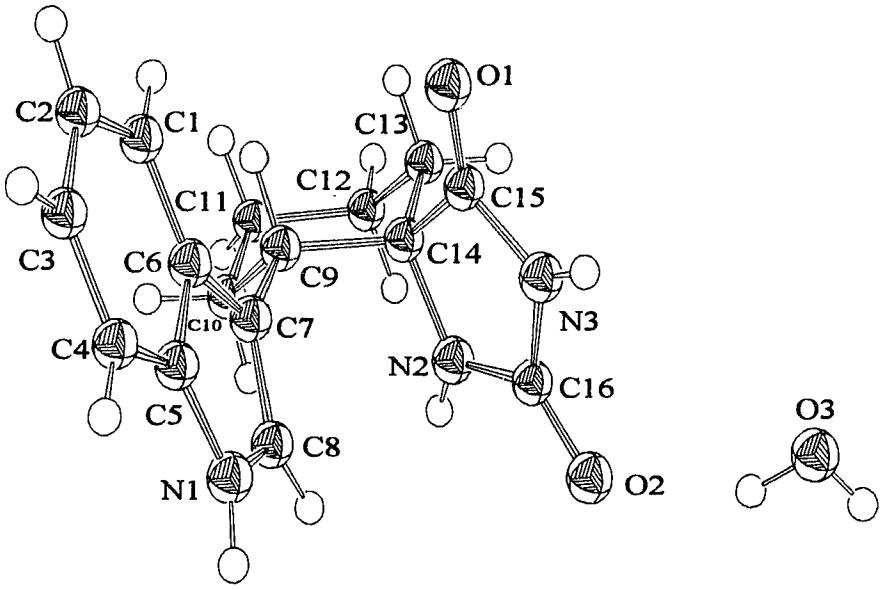


Figure III.2. ORTEP drawing of 2-(3-indolyl)cyclohexanespiro-5'-hydantoin

The hydrolysis of the above hydantoin was then attempted in a Parr® bomb with $Ba(OH)_2$ and deoxygenated water at 130 °C, 150 °C, and 200 °C with no success. When hydrolysis at 200 °C was attempted, after adjusting the pH of the aqueous phase to 7 and leaving the solution standing for 48 h, crystals were formed in the bottom of the test tube. X-ray analysis revealed that those crystals were not the expected constrained Trp derivative, but the starting hydantoin monohydrate, Figure III.2.

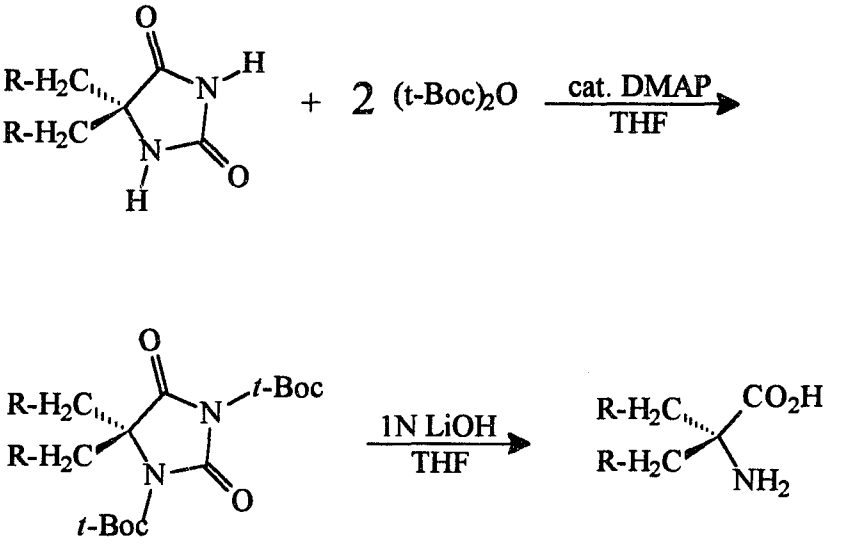
While the synthesis of this amino acid was in progress, Kubik and co-workers published a method to hydrolysize hydantoins under mild conditions.[81] In this article it is described that open-chain spirohydantoins were N-protected quantitatively with di-*tert*-butyl dicarbonate and a catalytic amount of DMAP in THF in 1 hour. The protected hydantoins were cleaved upon treatment with 1N LiOH in THF for 4 h to afford their corresponding amino acid derivatives with a 60-70% yield, Scheme III.4.

In order to test this procedure on cyclohexane systems, a model reaction was designed. Cyclohexanone was reacted with KCN and $(NH_4)_2CO_3$ in a solution of $MeOH/H_2O$ (1:1) at room temperature to afford cyclohexanespiro-5'-hydantoin with an 80% yield. The ^1H NMR spectrum showed the two amide protons at 10.45 and 8.37 ppm. The crystal structure of this hydantoin is depicted in Figure III.3.

Treatment of this cyclic hydantoin with di-*tert*-butyl dicarbonate and a catalytic amount of DMAP in THF afforded the di-N-substituted hydantoin quantitatively, mp = 151-152 °C. The ^1H NMR spectrum revealed the disappearance of the two amide protons and the appearance of the methyl protons of the two *t*-Boc groups as large singlets at 1.58 and 1.56 ppm. Hydrolysis of this di-protected hydantoin with 1N LiOH in THF afforded 1-amino-cyclohexane-1-carboxylic acid. The ^1H NMR spectrum showed the absence of the large singlet corresponding to the methyl protons of the two *t*-Boc groups. The ^{13}C

NMR spectrum recorded the carbonyl group at 181.49 ppm, and the four unique carbons of the cyclohexane system at 64.17, 34.77, 27.04, and 23.46 ppm.

Treatment of 2-(3-indolyl)cyclohexanespiro-5'-hydantoin with di-*tert*-butyl dicarbonate and a catalytic amount of DMAP in THF failed in protecting the amide units of the hydantoin moiety. The ^1H NMR spectrum showed only the disappearance of the indole proton at 10.80 ppm.



Scheme III.4. Hydrolysis of *t*-Boc reacted hydantoins with 1N LiOH

In order to fully react the hydantoin group, several reaction conditions on cyclohexanespiro-5'-hydantoin were explored. The first attempt involved a THF/pyridine solvent mixture and a catalytic amount of DMAP where the two bases were expected to enhance the amide proton-abstraction process.

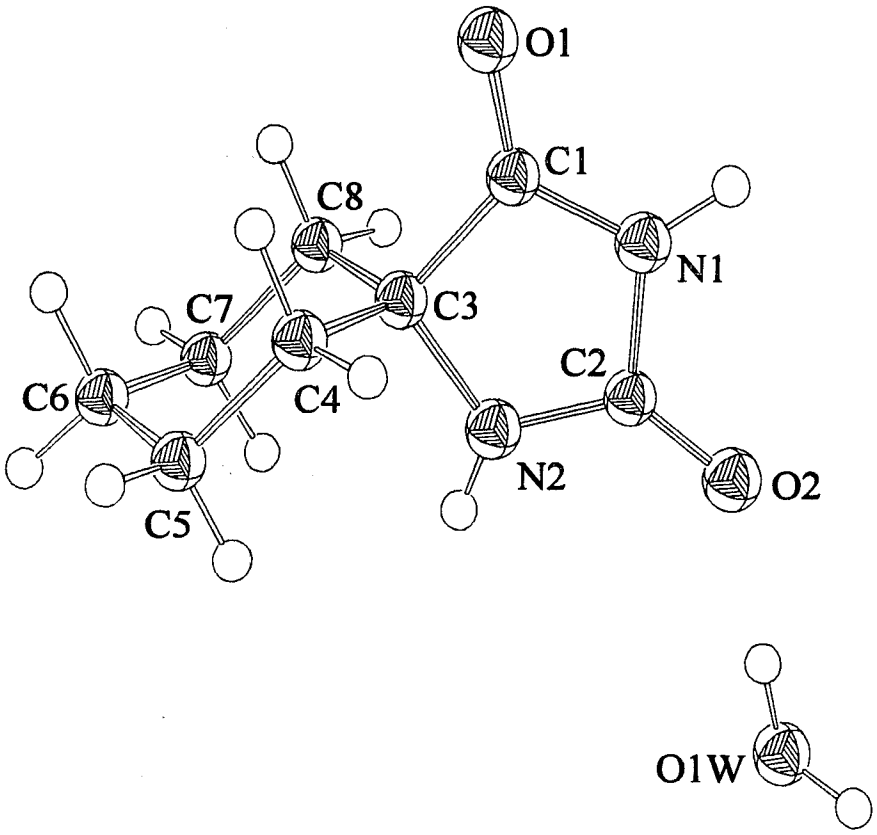


Figure III.3. ORTEP drawing of cyclohexanespiro-5'-hydantoin

The ^{1}H NMR spectrum recorded only the disappearance of the amide proton at 10.45 ppm (-CO-NH-CO-) and showed the unprotected amide proton as a singlet shifted downfield at 9.01 ppm, the methyl protons of the *t*-Boc group appeared as a large singlet at 1.48 ppm. In the second attempt, pyridine was used as solvent with a catalytic amount of DMAP. The ^{1}H NMR spectrum recorded a singlet at 9.02 ppm and a large singlet at 1.48 ppm proving that the protection reaction worked only partially. The next attempt involved the use of DBU, as the base, in THF. ^{1}H NMR showed a spectrum identical to the spectra obtained in the last two reactions.

Full protection of cyclohexanespiro-5'-hydantoin was finally achieved using 2.5 equivalents of di-*tert*-butyl dicarbonate and 2.5 equivalents of DBU in pyridine at room temperature for 1 hour. The ^{1}H NMR spectrum revealed the disappearance of both amido proton singlets and the presence of one large singlet at 1.48 ppm.

Treatment of 2-(3-indolyl)cyclohexanespiro-5'-hydantoin with di-*tert*-butyl dicarbonate and DBU in pyridine under the above reaction conditions, however, failed in protecting the two amidic sites. The ^{1}H NMR spectrum revealed the disappearance of the amide singlet (-CO-NH-CO) at 9.99 ppm and the presence of the indole and unprotected amide protons as singlets at 10.93 ppm and 9.10 ppm, respectively. This result suggests that steric factors between the indole group and the adjacent hydantoin unit keep the spiro amide group from being protected; consequently, only protection of the less hindered amide unit, in this case the CO-NH-CO unit, is achieved (Figure III.2, N3 atom).

Lastly, the hydrolysis was carried out at 250 °C finding at the end a homogeneous solution. This solutions was filtered, its pH adjusted to 7 with 1N HCl, and freeze-dried under high vacuum to give a white solid. This solid was desalted through ion exchange column and freeze-dried under high vacuum to afford a cream solid in a 27% yield. The ^{1}H NMR spectrum showed the dissapearance of the two hydantoin amide protons

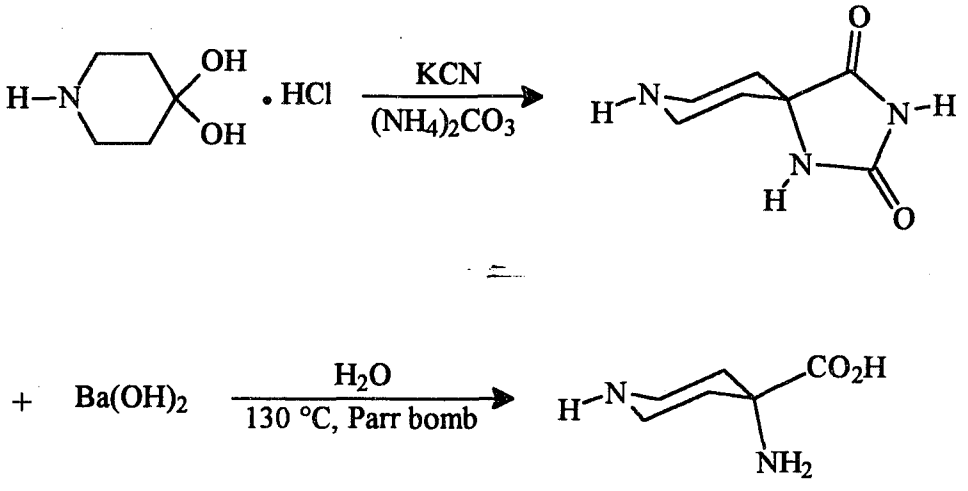
recording only the indole proton at 10.86 ppm, the proton on the cyclohexane carbon adjacent to the indole as a doublet of doublets at 3.54 ppm integrating for one proton, and four multiplets at 2.07, 1.78, 1.65 and 1.42 ppm integrating for 2 protons each. The ^{13}C NMR spectrum showed the carboxylic carbon at 173.53 ppm, the eight indole carbons between 136.57 and 111.48 ppm, and the cyclohexane carbons between 63.89 and 21.56 ppm. FAB spectroscopy showed a signal with a m+1 mass of 259 matching with the expected molecular mass of the protonated amino acid.

III.1.2 Constrained Aib analogs.

The synthesis of 4-amino-N-(*t*-Boc)-piperidine-4-carboxylic acid started from commercially-available 4-piperidone derivatives. The first derivative synthesized in this series was 4-amino-piperidine-4-carboxylic acid. 4-Piperidinespiro-5'-hydantoin was synthesized by reacting commercially available 4-piperidone monohydrate hydrochloride with KCN and $(NH_4)_2CO_3$ in a solution of $MeOH/H_2O$ (1:1) at room temperature with an 80% yield. The ^1H NMR spectrum showed the two amide protons at 10.50 (-CO-NH-CO) and 8.47 (-NH-CO-) ppm, three protons of the piperidine system a doublet of triplets at 2.84, 2.67, and 1.69 ppm, and the fourth proton as a doublet at 1.39 ppm. All the protons of the piperidine system integrated for one proton. The ^{13}C NMR spectrum recorded the two carbonyl carbons of the hydantoin at 177.93 and 156.23 ppm, and the three carbons of the piperidine system at 60.94, 41.10, and 33.74 ppm.

This hydantoin was successfully hydrolyzed with $Ba(OH)_2$ in water at 130 °C in a Parr® bomb in a 65% yield, Scheme III.5. The ^1H NMR spectrum showed the disappearance of the amide protons and the presence of the piperidine moiety as multiplets at 3.47-3.29, 3.24-3.06, and 2.25-2.00 ppm. The first two multiplets integrated for one proton each, while the latter integrated for two protons. The ^{13}C NMR spectrum

recorded the carbonyl carbon at 182 ppm, and the piperidine carbons at 59.10, 42.72, and 32.12 ppm.



Scheme III.5. Synthesis of 4-amino-piperidine-4-carboxylic acid

Since this amino acid will be eventually incorporated into peptides, it will be necessary to protect the heteroatom of the cyclic system with a *t*-Boc protecting group and the amino group with an Fmoc group. To achieve this, both nitrogen atoms will have to be protected with a *t*-Boc group, the primary amine will have to be selectively deprotected to be further protected with an Fmoc group.

In order to simplify the amino-acid-protection process, it was essential to synthesize an N-protected 4-piperidone analog which, after hydantoin-formation/base-hydrolysis, would lead to a 4-amino-N-protected-1-carboxylic acid derivative. Due to peptide synthesis purposes, it was decided the ideal candidate would be a *t*-Boc-protected piperidine analog.

Commercially available 4-piperidone monohydrate hydrochloride was first treated with 1.5 equivalents of Et_3N and 1.1 equivalents of DMAP in THF for 5 min at room temperature. Then 1.2 equivalents of di-*tert*-butyl dicarbonate was added and the mixture was stirred for 12 h at room temperature to afford N-(*t*-Boc)4-piperidone with a 70% yield. GC-MS analysis showed the presence of only one compound with a m/z of 199, matching the mass of the expected product. The ^1H NMR spectrum recorded the protons of the piperidine system as two triplets at 3.71 and 2.44 ppm, and the protons of the methyl group in the *t*-Boc unit as a large singlet at 1.42 ppm. The ^{13}C NMR spectrum showed the two carbonyl groups at 207.69 and 154.53 ppm, and the piperidine and *t*-Boc carbons at 80.43, 43.07, 41.20, and 28.43 ppm.

This keto derivative was reacted with KCN and $(NH_4)_2CO_3$ in a solution of $MeOH/H_2O$ (1:1) at 60 °C to afford N-(*t*-Boc)-4-piperidinespiro-5'-hydantoin in a 60% yield. The ^1H NMR spectrum recorded the protons of the hydantoin group at 10.71 and 8.47 ppm. and the characteristic protons of the *t*-Boc unit at 1.48 ppm. The ^{13}C NMR spectrum showed the three carbonyl units at 177.68, 156.45, and 153.79 ppm; and the carbons of the piperidine and *t*-Boc moieties at 78.85, 60.03, 32.63, and 27.97 ppm.

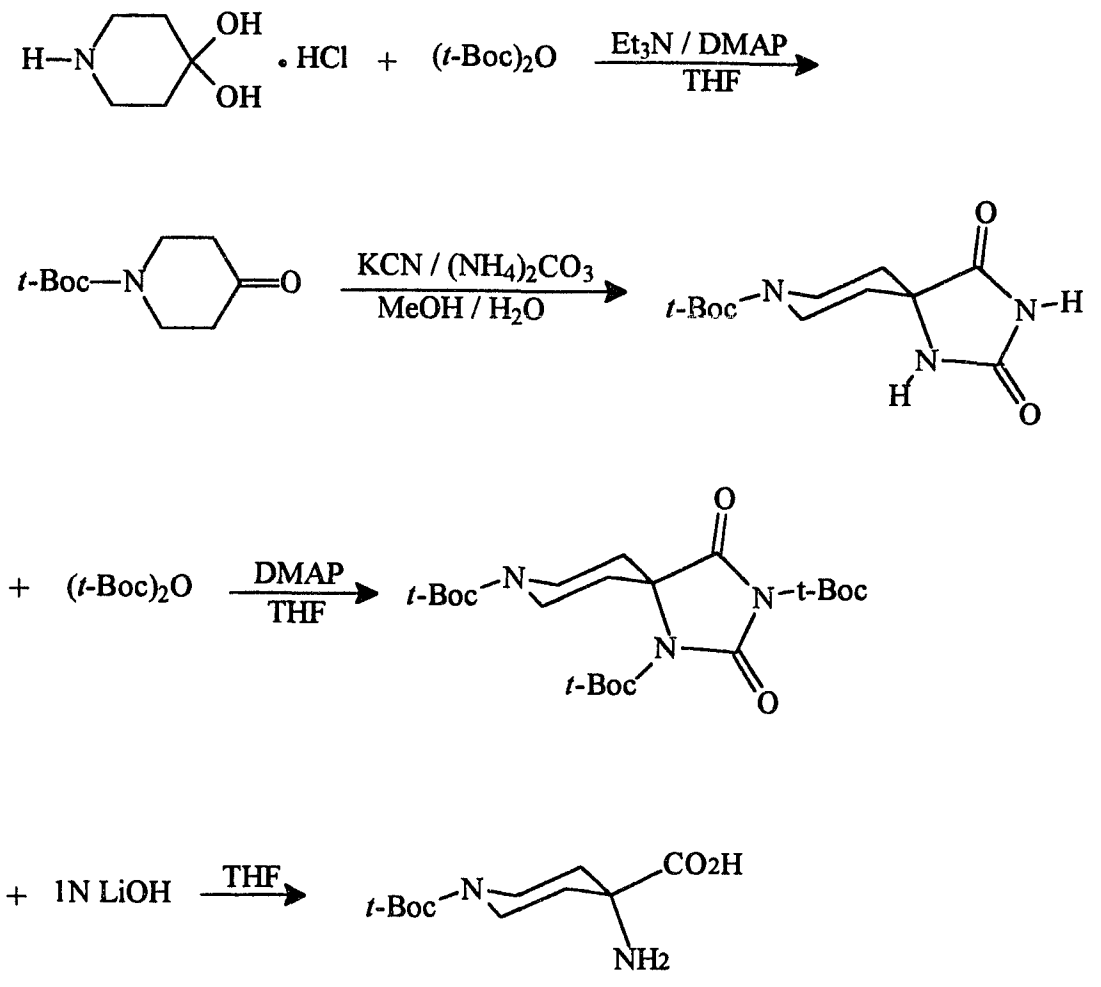
Basic hydrolysis of N-(*t*-Boc)-4-piperidinespiro-5'-hydantoin with 1N LiOH afforded 4-amino-N-(*t*-Boc)-piperidine-4-carboxylic acid, Scheme III.6.

III.2. SYNTHESIS OF BENZ[*F*]INDOLE DERIVATIVES.

III.2.1 Background.

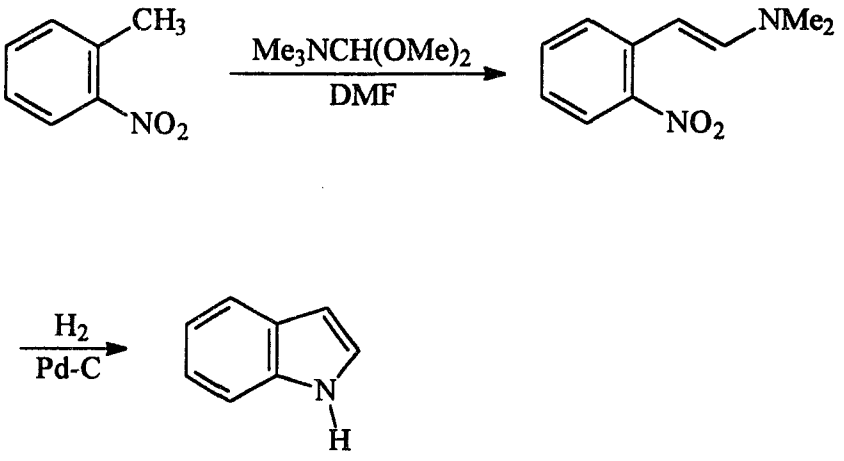
III.2.1.1 The Leimgruber-Batcho indole synthesis.

The Leimgruber-Batcho reaction is an indole synthesis based on the one-carbon-extension chain of the methyl unit in *o*-nitrotoluene via condensation with N,N-dimethylformamide dimethyl acetal to produce a *trans*-β-dimethylamino-2-nitrostyrene intermediate.



Scheme III.6. Synthesis of 4-amino-N-(*t*-Boc)-piperidine-4-carboxylic acid

Reduction of the nitro group accompanied by in situ ring closure afforded indole with excellent yields, Scheme III.7. This method and its various modifications are widely used to synthesize indole and Trp derivatives.[82,83,84,85,86,72,63,87,88,89]



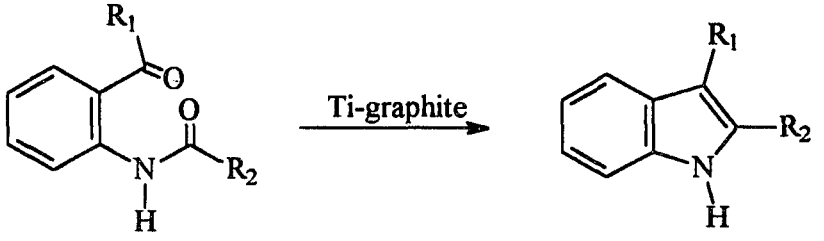
Scheme III.7. The Leimgruber-Batcho indole synthesis

III.2.1.2 Transition-metal-promoted synthesis.

Synthesis of indole and Trp analogs via transition-metal-promoted coupling/cyclization reactions is now a focus of attention.[90] Recently, all efforts have concentrated mainly in the use of three metals for indole and Trp synthesis: Ti, Cu, and Pd.

Fürstner and Jumbam developed a synthetic route based on the McMurry's low-valent titanium reaction. The McMurry reaction[91,92] is widely used to form alkenes via reductive coupling of carbonyl compounds allowing not only the formation of strained olefins, but also the access to cyclic products of almost any ring size when applied to

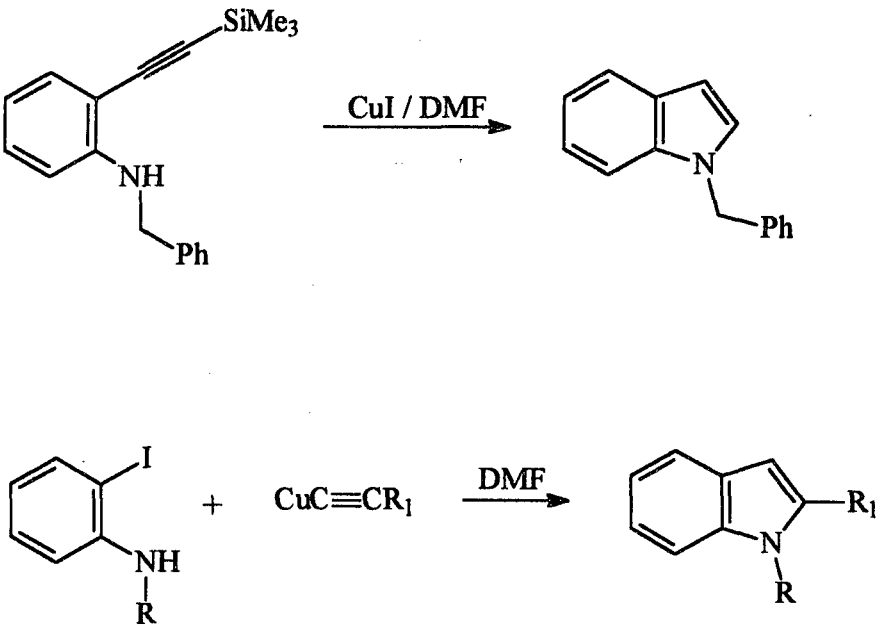
dialdehydes, ketoaldehydes or diketones.[93,94,95] Cyclization of acylamido carbonyl compounds with Ti on graphite affords indole derivatives in good to excellent yields,[96] Scheme III.8.



Scheme III.8. Titanium-induced synthesis of indoles

Indole derivatives have been successfully made using copper(I) acylides in moderate yields. This synthesis is achieved in two steps. First, *o*-iodoaniline is coupled with copper acetylides in DMF. The resulting alkyne intermediate is then cyclized with CuI and $CaCO_3$ in DMF to furnish indole. The major disadvantage of this methodology is its limitation to provide only 2-substituted indoles,[97,98] Scheme III.9.

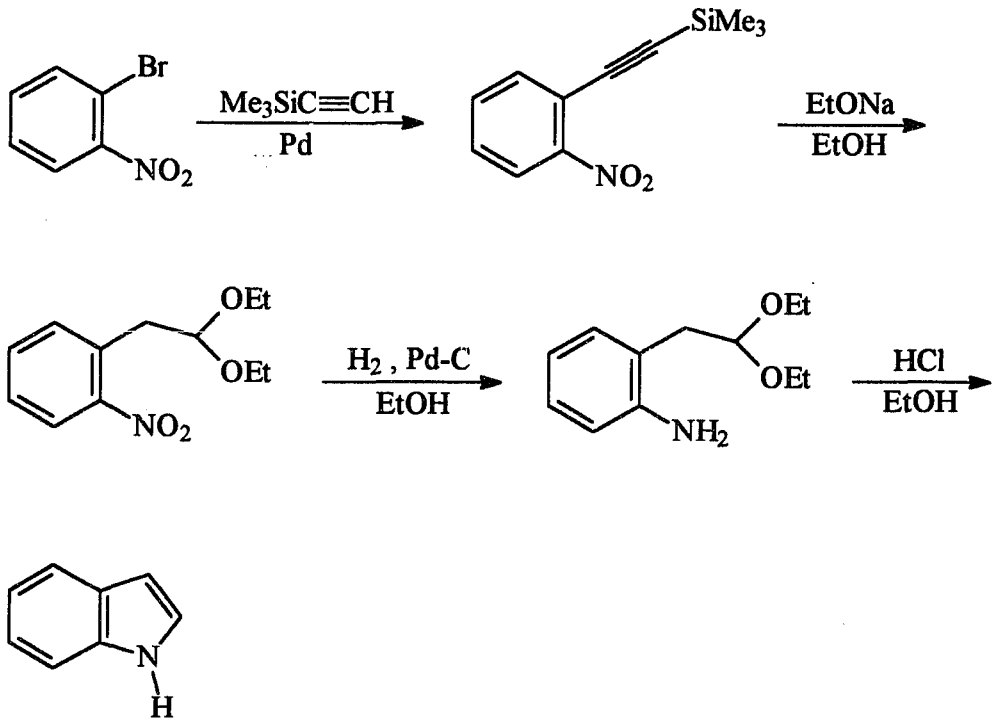
Sakamoto and co-workers used for the first time palladium in an indole synthesis to couple catalytically trimethylsilylacetylene to 2-bromonitrobenzene affording a terminal-silylated alkyne intermediate. This alkyne derivative was successfully transformed into indole after treatment with EtONa/EtOH, H_2 on Pd-C, and HCl/EtOH, respectively. Shortly after, in a similar manner, Sakamoto's team reported the synthesis of indole derivatives via palladium-coupling-catalysis between trimethylsilylacetylene and ethyl *o*-bromophenylcarbamate.[99,100] See Scheme III.10.



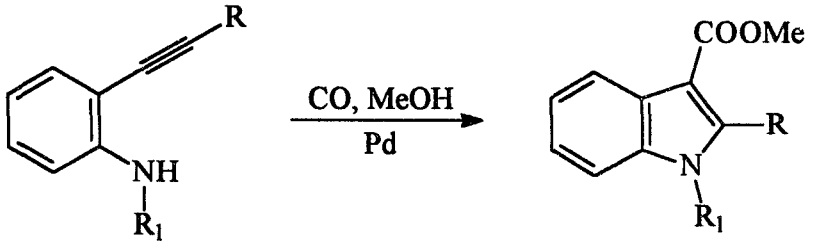
Scheme III.9. Copper(I)-promoted 2-substituted indole synthesis

Nowadays, Pd is the metal of choice to synthesize the indole framework and constrained indole and Trp derivatives in a Heck-like palladium-catalyzed cyclization fashion.[101,102,103,104,105,106] The Heck reaction is a highly efficient palladium-catalyzed coupling reaction of haloarenes and haloalkenes with alkenes. The high chemoselectivity and mild reaction conditions associated with low toxicity and costs of the reagents make the Heck reaction the tool of choice for C-C bond formation.[107,108,109]

Recently, N-protected *o*-alkynyl-aniline derivatives were cyclized with CO in presence of catalytic amounts of Pd to afford 2- and 2,3-substituted indole derivatives in moderate yields.[110,111,112] In a similar fashion, 2-halo-N-(2-propenyl) aniline derivatives underwent palladium-catalyzed cyclization to afford their corresponding indole analogs with excellent yields,[113,114] Scheme III.11.



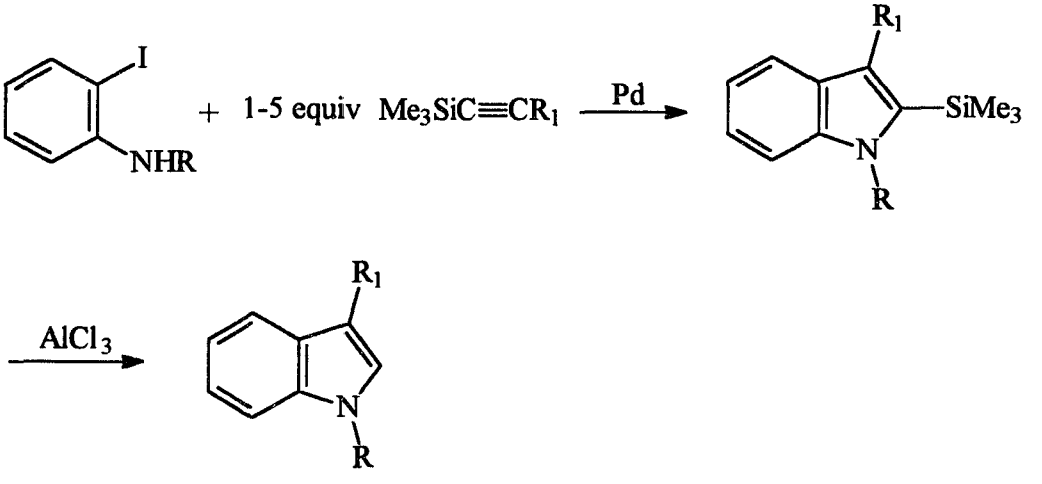
Scheme III.10. Mediated Pd-coupling reaction in the synthesis of indole



Scheme III.11. Pd-catalyzed cyclizations of N-protected *o*-alkynyl and 2-halo-N-(2-propenyl) aniline derivatives

The first one-pot indole synthesis via palladium-catalyzed cyclization reaction was recently developed by Larock.[115] In this work a wide variety of unsymmetrical alkynes were successfully inserted and cyclized regioselectively with N-protected-*o*-iodoanilines in presence of $Pd(OAc)_2$ in DMF to afford their corresponding indole analogs with good to excellent yields. In fact, it was observed that the more sterically bulky group of the alkyne ends up nearer the nitrogen atom in the indole product. Consequently, the more sterically bulky the group on the alkyne is, the more regioselective the cycloaddition is,[115] Scheme III.12.

Larock's breakthrough has become the cornerstone in indole and Trp synthesis and its scope and limitations are being currently explored.[116,117,118]



Scheme III.12. One-pot indole synthesis via Pd-catalyzed cyclization reaction

III.2.2. Synthesis of Benz[*f*]indole.

Two routes were explored to synthesize benz[*f*]indole and its corresponding derivatives. Both routes involve a naphthalene derivative bearing two substituents at the second and third position. These substituents after further transformations would form the pyrrole moiety providing the benz[*f*]annulated isomer. Commercially available 2-methylnaphthalene-bis(hexachlorocyclopentadiene) adduct was nitrated with fuming nitric acid for 30 min to afford exclusively the 3-methyl-2-nitronaphthalene derivative in good yields. ^{1}H NMR recorded the aromatic protons as two uncoupled sharp singlets at 8.41 and 7.73 ppm each one integrating for one proton, and the methyl protons as a sharp singlet at 2.65 ppm integrating for 3 protons. X-ray analysis corroborated the incorporation of the nitro group at position 3 on the aromatic system (Figure III.4).

2-Methylnaphthalene was not suitable for the synthesis of 3-methyl-2-nitronaphthalene because nitration on this substrate occurs mainly on position 1. The 2-methylnaphthalene-bis(hexachlorocyclopentadiene) adduct nitrates at position 3 due to steric factors. Regeneration of the aromatic naphthalene system was achieved via high vacuum pyrolysis (retro Diels-Alder) at 350 °C affording 3-methyl-2-nitronaphthalene quantitatively along with 2 equivalents of hexachlorocyclopentadiene, Scheme III.13.

As in 2-nitrotoluene, the nitro group in 3-methyl-2-nitronaphthalene is expected to increase the acidity of the adjacent methyl group. So, refluxing 3-methyl-2-nitronaphthalene with 10 equivalents of pyrrolidine and 10 equivalents of N,N-dimethylformamide dimethyl acetal in anh. DMF extended the carbon chain of the methyl group to a mixture of 2-(3-nitro-2-naphthyl)1-(N-pyrrolidinyl)ethene and 2-(3-nitro-2-naphthyl)1-(N,N-dimethyl)ethene. This conclusion is supported by the disappearance of the ^{1}H NMR signal of the methyl singlet of the starting material at 2.71 ppm. Reduction

of this mixture with Raney Ni or hydrogen over Pd/C provided benz[*f*]indole with a 13% yield, Scheme III.14.

The first synthesis of benz[*f*]indole was established in 1953 when Süs and co-workers claimed its synthesis via ring-contraction on 4-oxo-3-diazo-6,7-benzoquinoline to obtain benz[*f*]indole-3-carboxylic acid which, after decarboxylation at 230 °C, gave benz[*f*]indole.[119] The authors only reported melting point and elemental analysis of the solid without citing yields. Furthermore, no evidence was presented to verify that they had the benz[*f*]annulated isomer, Scheme III.15.

In 1986 Sakamoto and co-workers[120] reported that the ethyl carbamate derivative of 3-bromo-2-naphthylamine[121] was coupled with trimethylsilylacetylene in presence of dichlorobis(triphenylphosphine)palladium, CuI, and Et_3N in a sealed tube at 80 °C for 2 h. to produce a 3-alkynyl-2-carbamate intermediate which upon treatment with sodium ethoxide in ethanol afforded benz[*f*]indole in 48% overall yield from the 3-bromo-2-naphthylcarbamate, Scheme III.16.

The latest reported synthesis of benz[*f*]indole appeared in 1993 by Watanabe and co-workers.[122] The synthesis consisted of treating ethyl pyrrole-2-carboxylate with phthalic anhydride and aluminum chloride to give a keto acid intermediate that upon treatment with triethylsilane and TFA was reduced to a pyrrolyl-benzoic acid derivative. The carboxylic acid group was reduced with $NaBH_4$ to its corresponding alcohol derivative.

Further oxidation with MnO_2 provided an aldehyde intermediate which in the presence of TFA underwent cyclization affording ethyl benz[*f*]indole-2-carboxylate. Hydrolysis of this ester with KOH in EtOH followed by decarboxylation gave benz[*f*]indole, Scheme III.17.

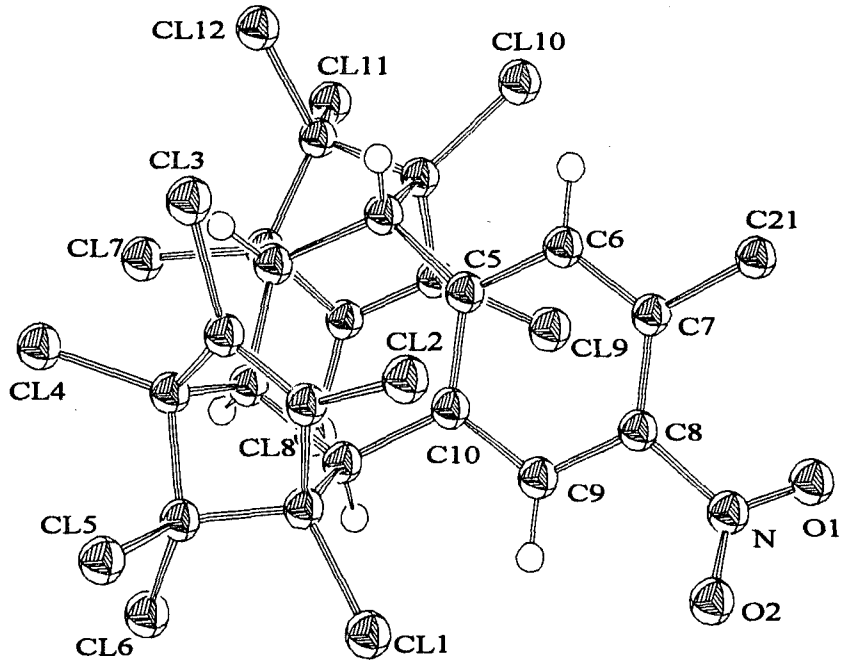
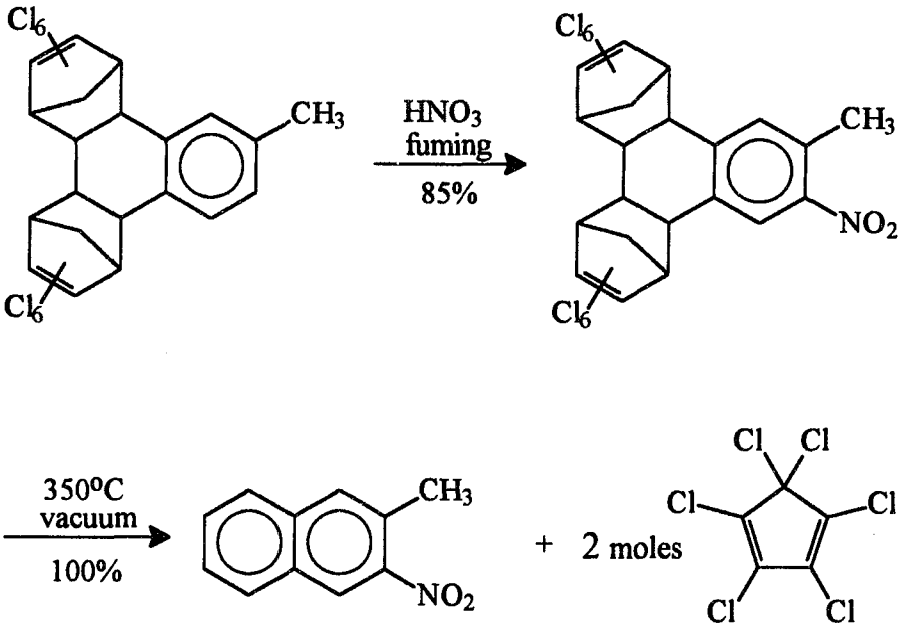
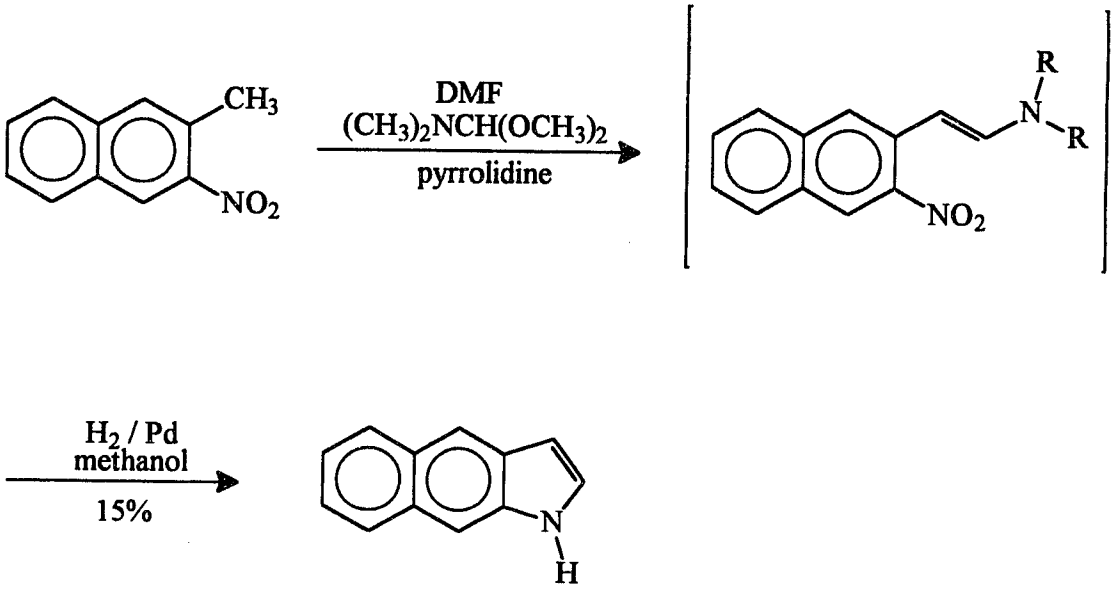


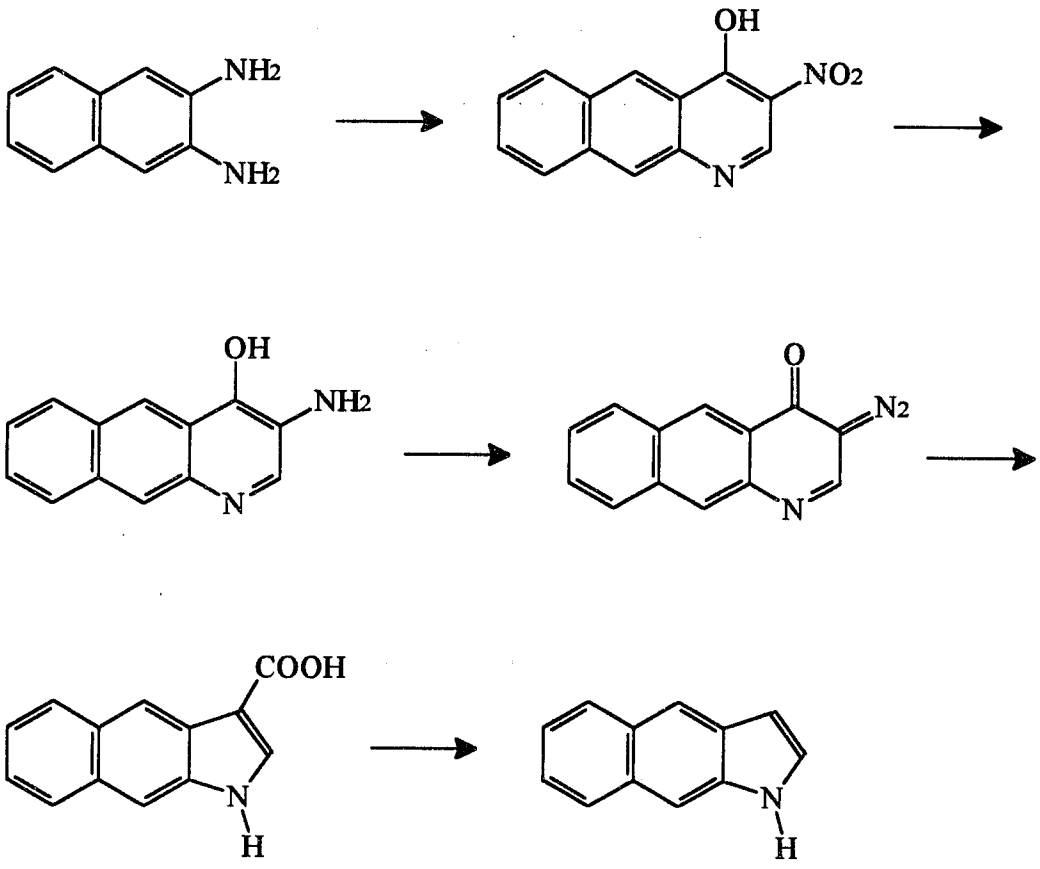
Figure III.4. ORTEP drawing of 3-methyl-2-nitro-naphthalene-bis(hexachlorocyclopentadiene) adduct



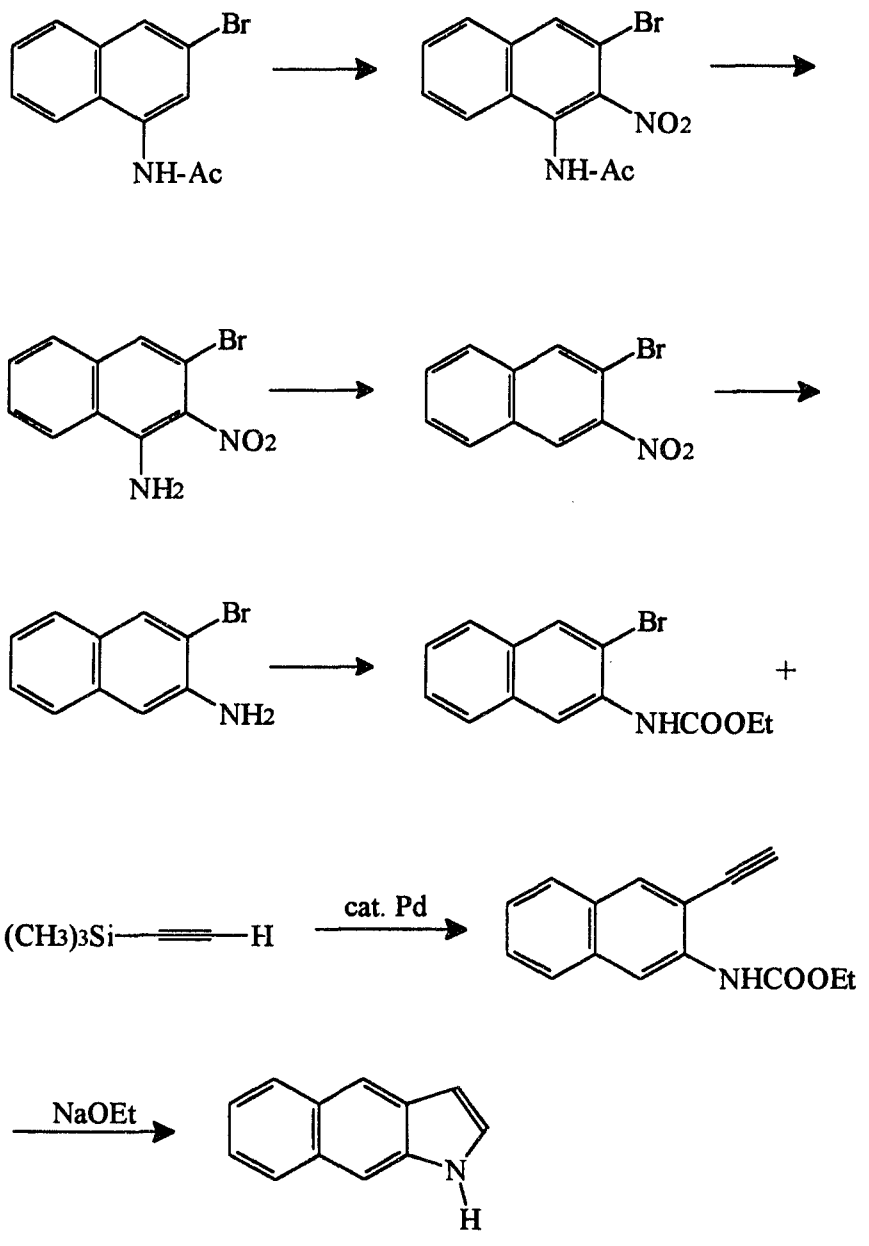
Scheme III.13. Synthesis of 3-methyl-2-nitronaphthalene



Scheme III.14. Synthesis of benz[*f*]indole



Scheme III.15. Süs' benz[*f*]indole synthesis



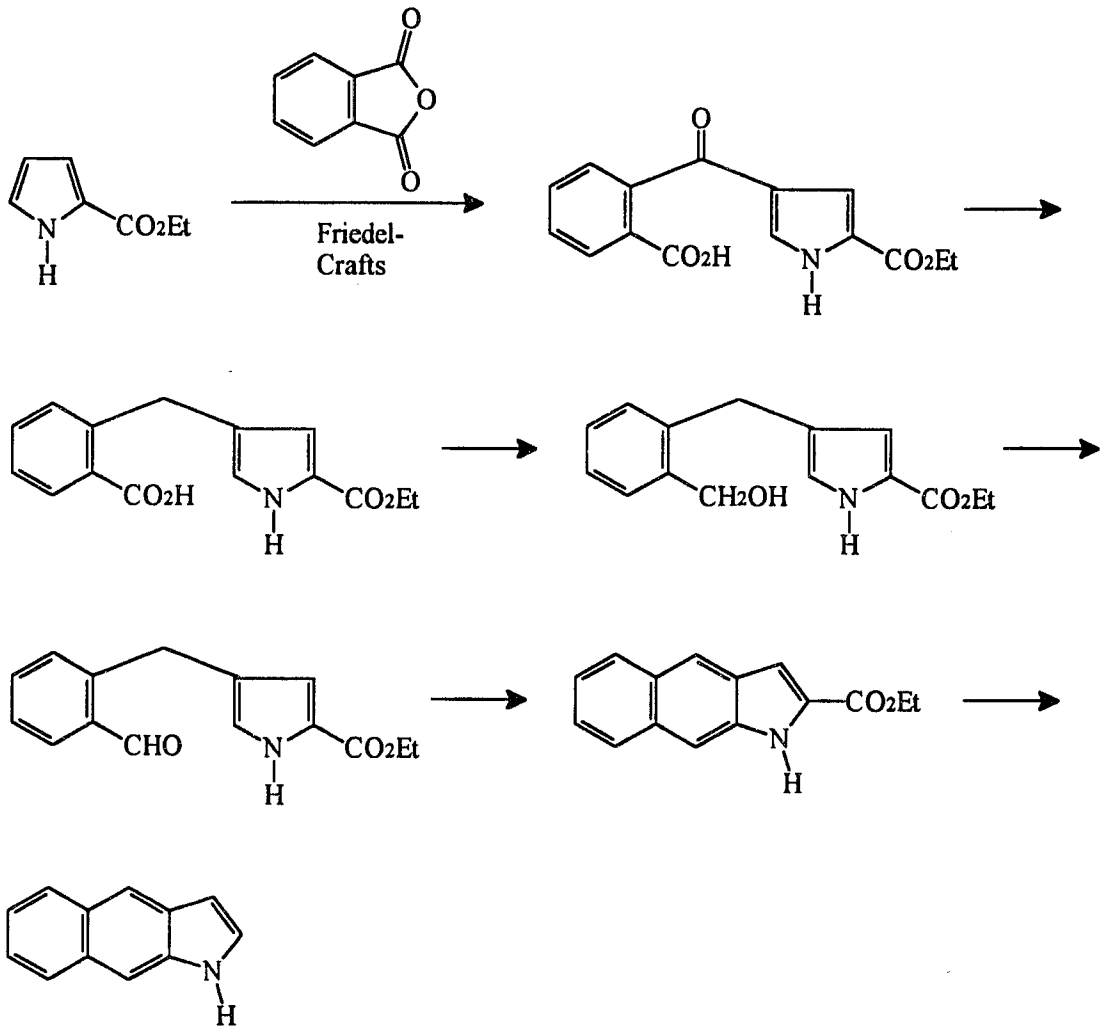
Scheme III.16. Sakamoto's benz[*f*]indole synthesis

All these synthetic methods provide benz[*f*]indole; however, they involve a long synthetic route. In this study, despite the low yield, the methodology developed is to date, by far, the shortest synthetic route to form benz[*f*]indole (see Scheme III.14).

In order to optimize the synthesis of the 2-(3-nitro-2-naphthyl)1-(N-pyrrolidinyl)/(N,N-dimethyl)ethene intermediates several reaction conditions were varied (solvent, reactant ratios, and temperature); however, all attempts to improve the yield failed.

III.2.3 Synthesis of Benz[*f*]tryptophan.

Using a similar strategy, while still expecting to overcome the low-yield formation of the above mixture of enamines, the synthesis of benz[*f*]tryptophan was pursued. The transformation of 2-nitrotoluene into an acrolein derivative provides a species that undergoes Michael addition with sodium diethyl formamidomalonate anion to give an N-formyl-pyrrolidine intermediate which upon hydrogenation produces a Trp derivative.In the same fashion 3-methyl-2-nitronaphthalene was converted into α-(3-nitro-2-naphthyl)acrolein when the 2-(3-nitro-2-naphthyl)1-(N-pyrrolidinyl)/(N,N-dimethyl)ethene mixture was treated with 40% aq. dimethylamine, 37% aq. formaldehyde, glacial acetic acid, and anh. methanol. Unfortunately, the yield was low as in the synthesis of benz[*f*]indole; α-(3-nitro-2-naphthyl)acrolein was afforded in only a 14% yield. Two sharp singlets at 6.66 and 6.39 ppm, with an integration area corresponding to one proton each, confirm the presence of the two vinyl protons. Also, a sharp singlet at 9.75 ppm, with an integration area corresponding to one proton, verifies the presence of the aldehyde group.



Scheme III.17. Watanabe's benz[*f*]indole synthesis

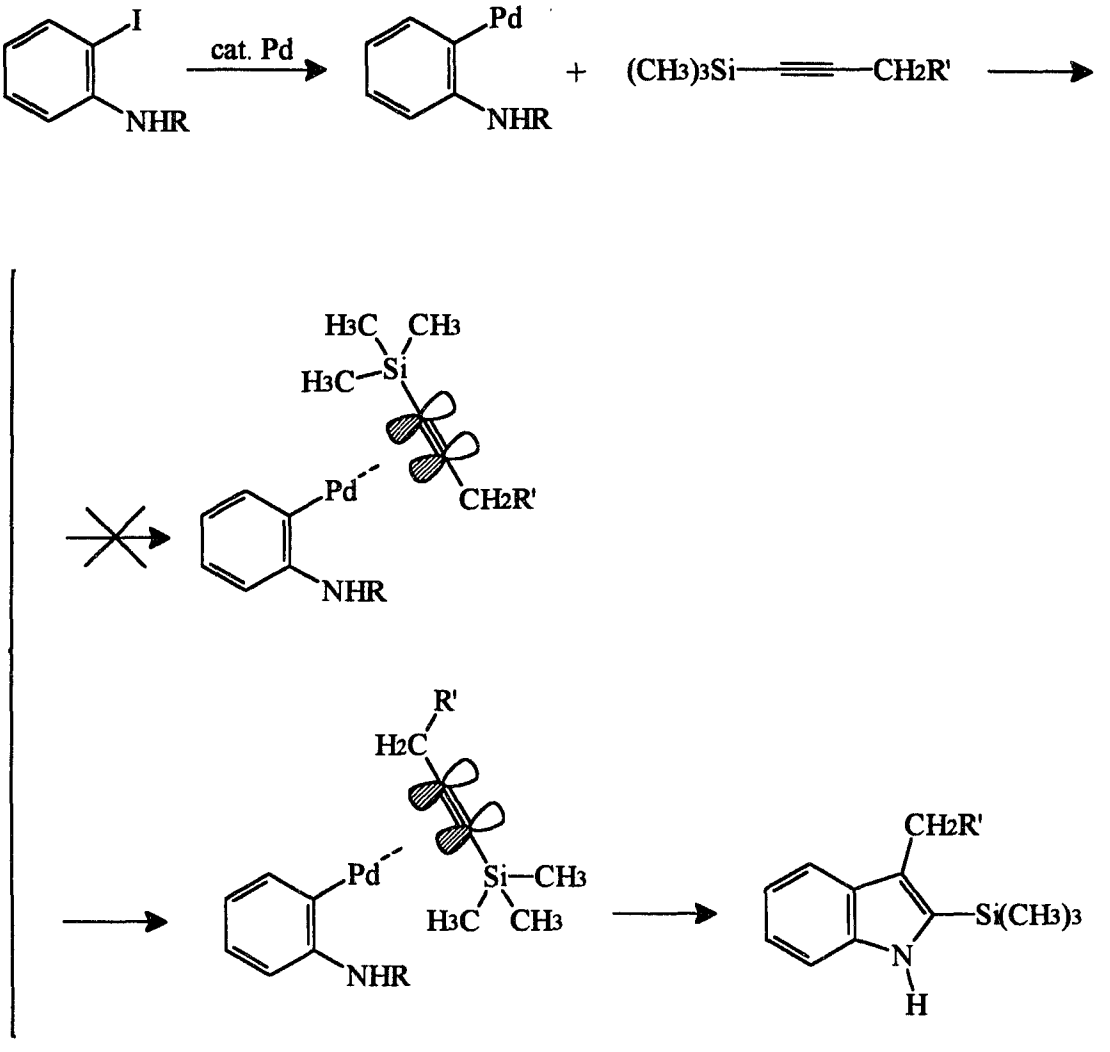
Since the low-yield formation of the 2-(3-nitro-2-naphthyl)1-(N-pyrrolidinyl)/(N,N-dimethyl)ethene intermediates was a bottleneck for the synthesis of both benz[*f*]indole and benz[*f*]tryptophan, an alternative strategy was investigated.

Indole and Trp have been recently synthesized via a palladium-catalyzed reaction between 2-iodoaniline and various terminal-silylated alkyne derivatives. In this case palladium forms an organometallic intermediate of the type C-Pd- which, upon interaction with the π orbitals of the alkyne system, attracts the alkyne with the silylated side oriented away from the aromatic part of the Pd complex. Consequently, when cyclization takes place a 2-trimethylsilylated indole intermediate is selectively formed, Scheme III.18.

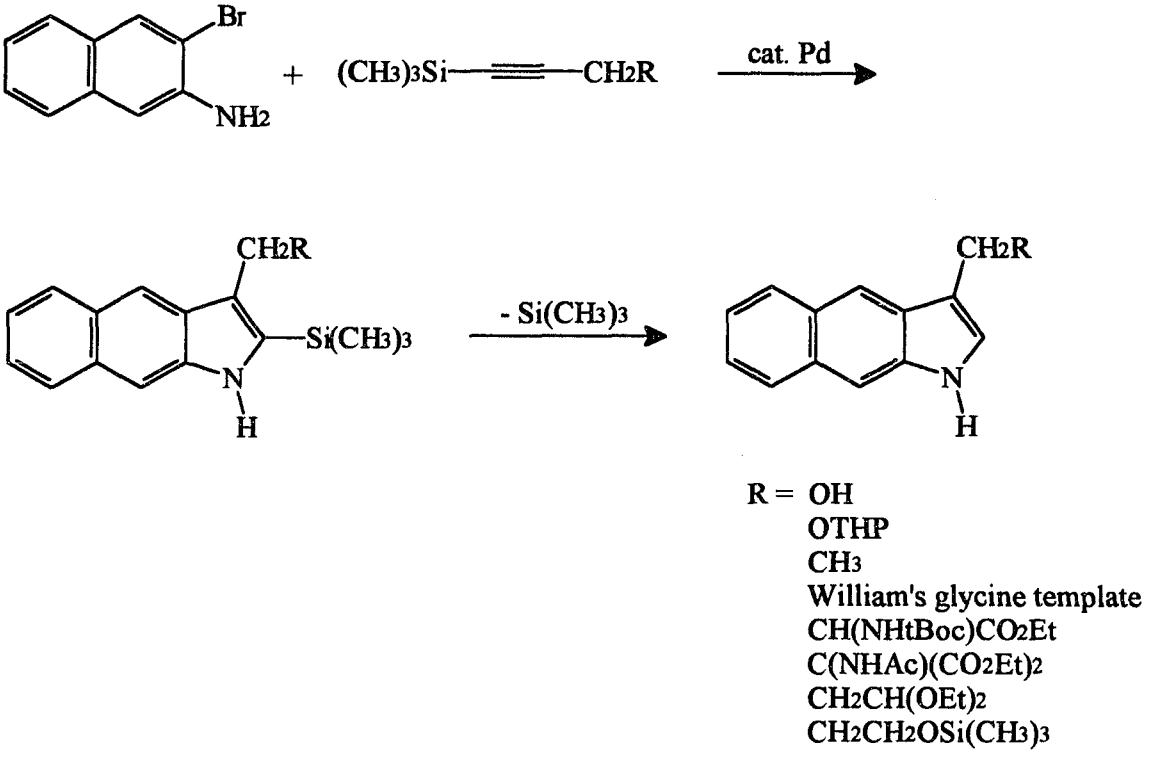
A 2,3-disubstituted naphthalene derivative is essential for the formation of the benz[*f*]annulated framework using this synthetic approach. This synthesis of the benz[*f*]tryptophan is based on a palladium-catalyzed cyclization reaction between 3-bromo-2-aminonaphthalene and a terminal-silylated alkyne derivative, Scheme III.19.

Commercially available 2-bromo-3-nitronaphthalene-bis(hexachlorocyclopentadiene) adduct underwent high vacuum pyrolysis (retro Diels-Alder) at 350 °C to afford 2-bromo-3-nitronaphthalene quantitatively along with 2 equivalents of hexachlorocyclopentadiene. Reduction with $SnCl_2$ dihydrate and conc. HCl in isopropanol afforded 3-bromo-2-aminonaphthalene hydrochloride. The crude hydrochloride was refluxed with sat. aq. Na_2CO_3 for 6 h to afford 3-bromo-2-aminonaphthalene with a 70% yield.

A model reaction for the cyclization reaction was carried out using commercially available *o*-iodoaniline and propargyl alcohol under previously reported conditions. Freshly recrystallized *o*-iodoaniline was mixed with 2 equivalents of propargyl alcohol, 1 equivalent of n-Bu_4NCl, 2.5 equivalents of powdered Na_2CO_3, 10 mol% powdered PPh_3 and 10 mol% $Pd(OAc)_2$ in anh. DMF at 100 °C under argon for 24 h.



Scheme III.18. Indole formation via palladium-catalyzed cyclization reaction



Scheme III.19. Synthesis of 3-methyl substituted benz[*f*]indole derivatives

GC-MS analysis of the crude dark brown reaction mixture confirmed the presence of a major peak with a m/z of 204, which corresponds to the expected 2-trimethylsilyl-3-(methanol)indole after loss of a $-CH_3$ group.

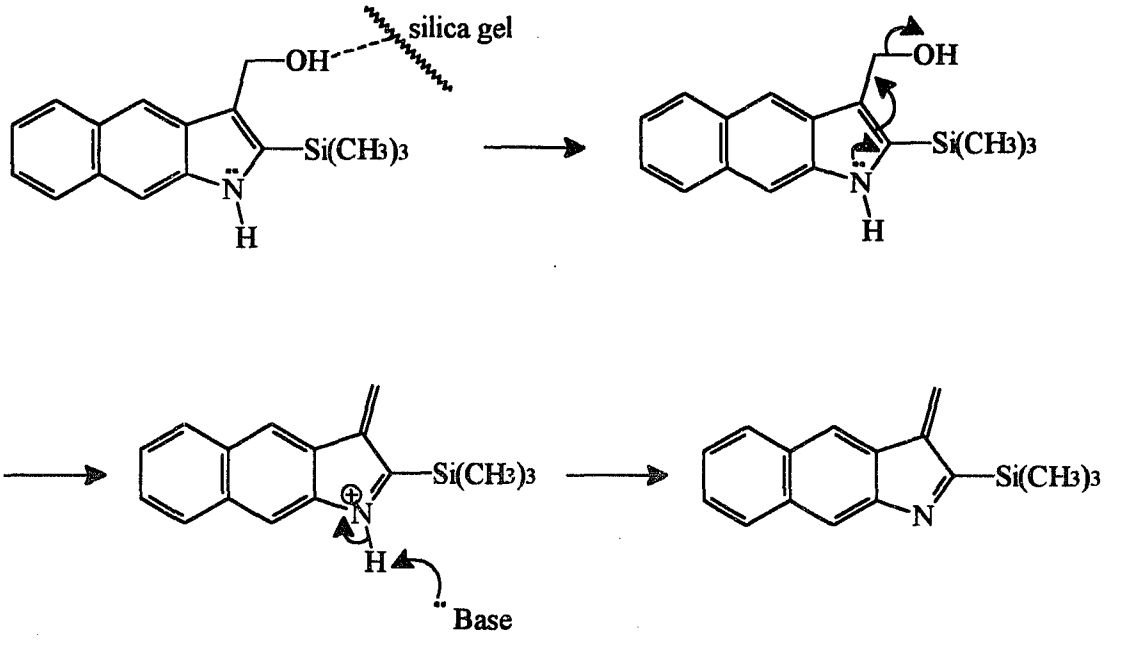
Treating 3-bromo-2-aminonaphthalene with the above reaction conditions afforded also a dark brown mixture. GC-MS analysis of the crude mixture showed only one peak with a m/z of 269, which corresponds exactly to the mass of 2-trimethylsilyl-3-(methanol)benz[*f*]indole. All attempts to purify the 2-trimethylsilyl indole and

benz[*f*]indole intermediates by column chromatography over silica gel failed due to decomposition in the column. It is very likely that the hydroxyl group is activated by the silica gel and is eliminated due to conjugation between the lone pair of electrons of the N heteroatom and the adjacent double bond, Scheme III.20.

At this point, the proper conditions for the cyclization reaction had been found, but the instability of the alcohol intermediates towards silica gel chromatography required a change in acetylene in order to avoid decomposition of the intermediates during the isolation.

The first alkyne explored was an alcohol-protected derivative of 3-trimethylsilylpropargyl alcohol. 3-(Tetrahydro-2-pyranyloxy)-1-(trimethylsilyl)propyne was synthesized by mixing commercially available propargyl alcohol with neat 3,4-dihydro-2*H*-pyran and a catalytic amount of *p*-toluenesulfonic acid at 50 °C for 5 h to afford a thick yellow oil which after high vacuum distillation afforded tetrahydro-2-(2-propynyloxy)-2*H*-pyran. Treatment of this alkyne with BuLi at 0 °C followed by trimethylchlorosilane gave 3-(tetrahydro-2-pyranyloxy)-1-(trimethylsilyl)propyne with a good overall yield. ^{1}H NMR of the final product in $CDCl_3$, without any internal standard, showed the disappearance of the proton of the terminal alkyne at 2.38 ppm as well as a huge singlet at 0.17 ppm integrating for 9 protons.

The next 3-trimethylsilylpropargyl alcohol analog made was 3-trimethylsilyl-2-propynyl *p*-toluenesulfonate. This compound was synthesized by treating commercially available 3-trimethylsilylpropargyl alcohol with freshly powdered KOH and freshly recrystallized *p*-toluenesulphonyl chloride in ether at -50 °C. As reported in the literature, 3-trimethylsilyl-2-propynyl *p*-toluenesulfonate was obtained initially as a colorless liquid.



Scheme III.20. Silica gel-promoted decomposition

However, after several recrystallizations from hexanes, the product was obtained as colorless needles. ^{1}H NMR showed that the singlet corresponding to the two propargyl protons was shifted downfield to appear at 4.72 ppm. Besides the characteristic sharp singlet of the methyl silane protons at 0.17 ppm, a singlet belonging to the methyl group of the tosylate was seen at 2.49 ppm. The presence of the aromatic unit was confirmed by two doublets, one at 7.84 and the other at 7.36. Furthermore, X-ray analysis on these needles confirmed that 3-trimethylsilyl-2-propynyl *p*-toluenesulfonate is indeed a solid, not a colorless liquid as stated in the literature[123,124] (Figure III.5).

3-(Tetrahydro-2-pyranyloxy)-1-(trimethylsilyl)propyne was made to obtain a 2-trimethylsilyl-benz[*f*]indole derivative that, upon treatment with PBr_3, would be expected

to produce a bromide intermediate that could be alkylated on the 3-methylene unit by glycine precursors to complete the benz[*f*]tryptophan framework. Moreover, an alternative approach, the potential of using terminal-silylated glycine-precursor-containing alkynes, was also explored.

Alkylation of 3-trimethylsilyl-2-propynyl *p*-toluenesulfonate with the commercially available William's glycine template *tert*-butyl (2*R*,3*S*)-(-)6-oxo-2,3-diphenyl-4-morpholine-carboxylate in anh. THF with bis(trimethylsilyl)sodium amide at 0 °C gave a mixture of C- and O-alkylated products. Although the ^{1}H NMR of the final mixture was rather complicated to interpret, two sharp singlets at 0.19 and 0.13, corresponding to the trimethylsilyl groups, supported the conclusion of C- and O-alkylation. In order to enhance C-alkylation a propargyl unit bearing a better leaving group had to be synthesized.

3-Trimethylsilylpropargyl alcohol was treated with *o*-phenylene phosphorochloridite in anh. pyridine for 12 h., followed by iodine at 0 °C in the absence of light to afford 3-trimethylsilylpropargyl iodide with a 50% yield. The ^{1}H NMR of this iodide possess a distinctive propargyl singlet at 3.70 ppm in addition to the large singlet at 0.15 ppm corresponding to the trimethylsilyl group. Alkylation of 3-trimethylsilylpropargyl iodide by the William's glycine template under the above reaction conditions provided enantiomerically pure C-alkylated product as a white solid with an 88% yield. The ^{1}H NMR spectrum of this compound showed the disappearance of the two propargyl protons at 3.70 ppm and the appearance of two newly formed diastereotopic protons of the propargyl unit as a doublet of doublets at 3.2-3.0 ppm along with the trimethylsilyl protons at 0.10 ppm. The ^{13}C NMR spectrum revealed the presence of the two carbonyl carbons at 169.16 and 154.11 ppm, the two alkyne carbons at 102.40 and 89.50 ppm, the

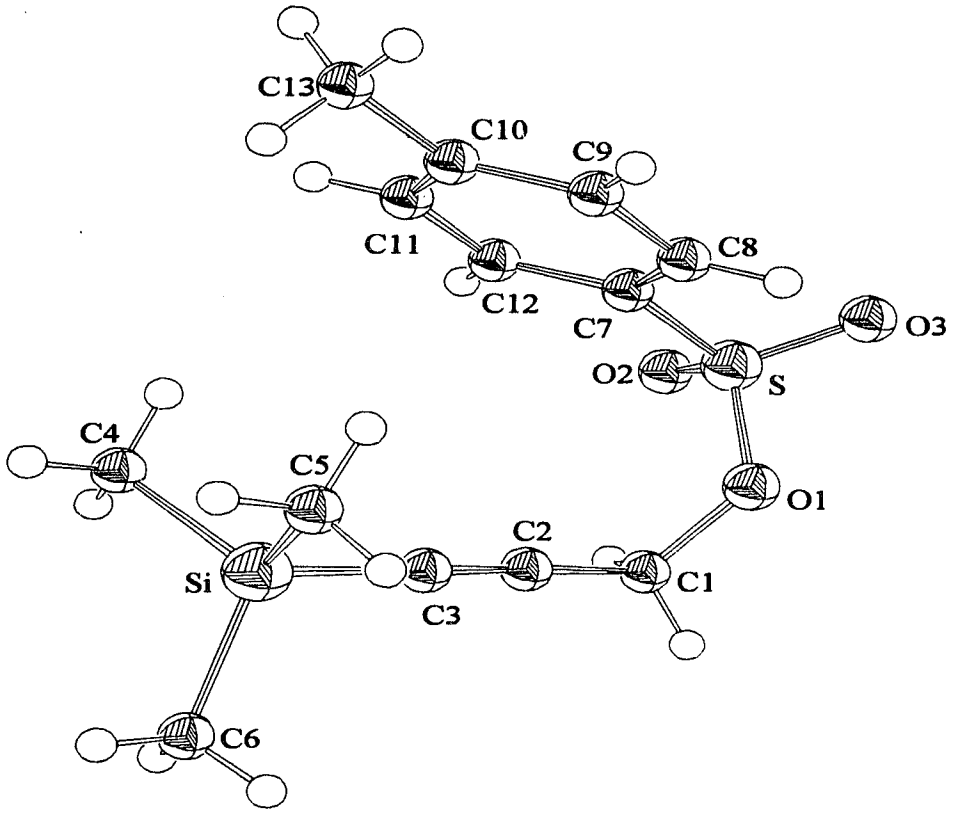
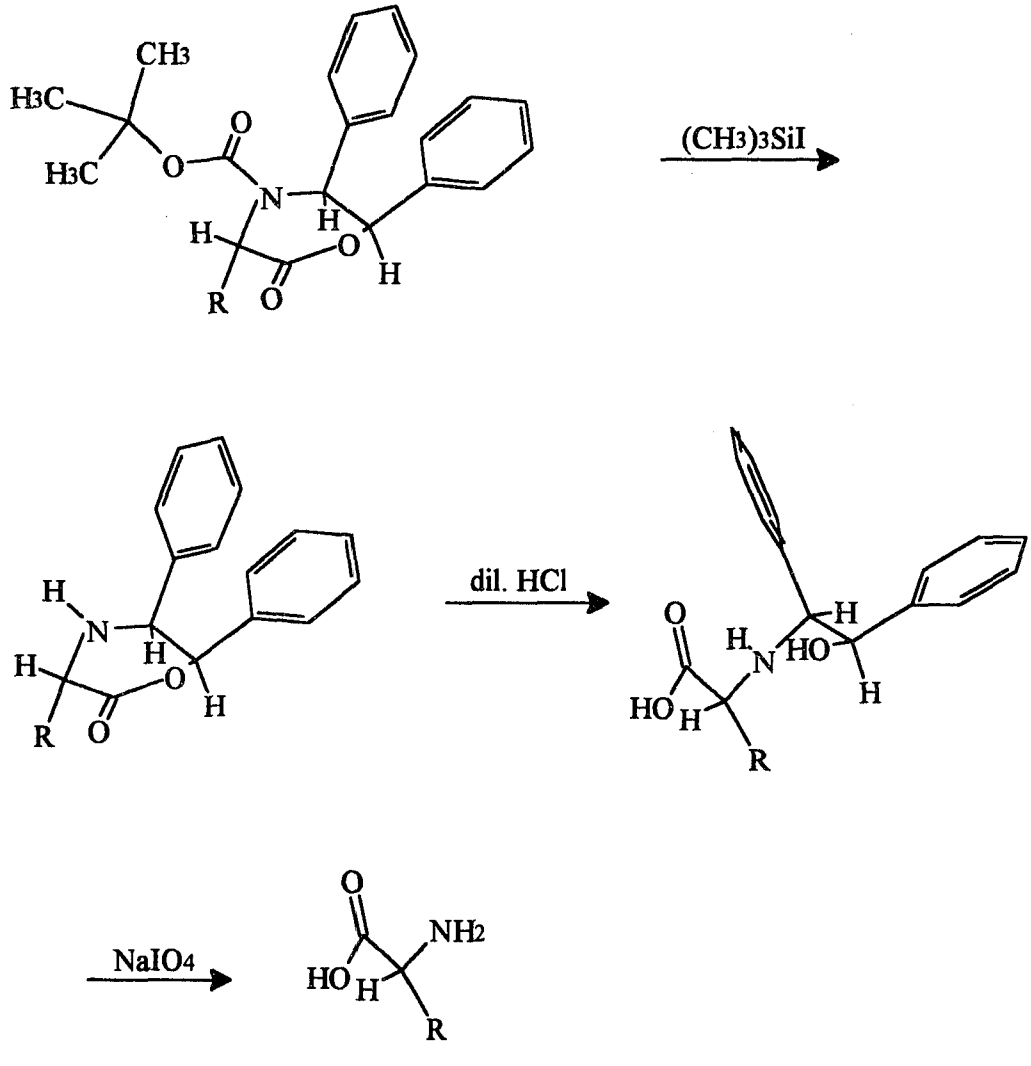


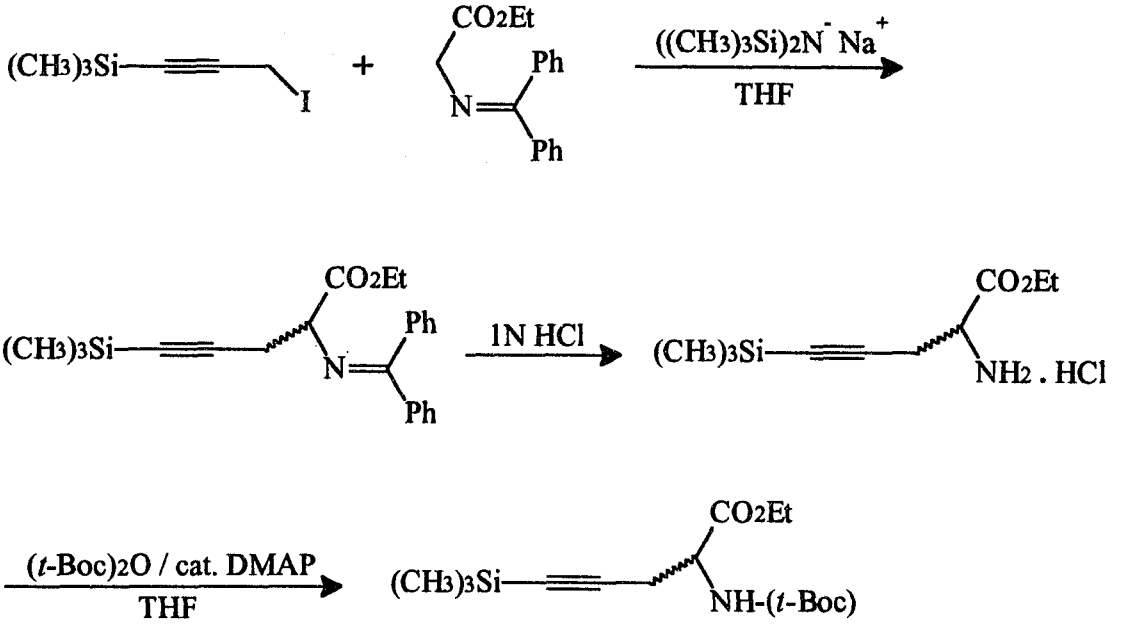
Figure III.5. ORTEP drawing of 3-trimethylsilyl-2-propynyl *p*-toluenesulfonate

methyl carbons of the *t*-Boc group at 28.05 ppm, and the methyl carbons of the trimethylsilyl group at 0.147 ppm. α-Alkylated William's templates are very useful because they give enantiomerically pure α-alkylated glycine derivatives; however, a multistep deprotection reaction sequence (N-deprotection, lactone ring-opening, and benzylic oxidation) is required,[61] Scheme III.21.



Scheme III.21. William's template deprotection sequence

In order to avoid possible complications between the above deprotection reaction sequence and the benz[*f*]indole framework, other glycine precursors that are easier to deprotect, were used to alkylate the propargyl unit. 3-Trimethylsilylpropargyl iodide was treated with ethyl N-(diphenylmethylene)glycinate and bis(trimethylsilyl) sodium amide in anh. THF at -78 °C to produce an orange oil. This oil was taken up in THF, treated with aq. 1N HCl and concentrated to dryness to obtain its corresponding amino hydrochloride salt. This hydrochloride was treated with di-*tert*-butyl dicarbonate in anh. THF in presence of a catalytic amount of DMAP to afford ethyl N-(*t*-Boc)-4-(trimethylsilyl)-4-pentynoate as a light orange oil in an overall yield of 46%, Scheme III.22.



Scheme III.22. Synthesis of ethyl N-(*t*-Boc)-4-(trimethylsilyl)-4-pentynoate

The ^{1}H NMR spectrum of this alkyne derivative shows the characteristic sharp singlet of the methylsilyl protons at 0.13 ppm as well as the large sharp singlet of the methyl protons in the *tert*-butyl unit of the *t*-Boc component at 1.41 ppm. The two propargyl protons appeared as a doublet of triplets at 2.74 ppm. Furthermore, GC-MS analysis revealed the presence of a single compound with a m/z of 256 which corresponds to the molecular mass of the expected product (313) after loss of a $(CH_3)_3C$- unit. ^{13}C NMR shows the presence of 2 carbonyl units at 170.88 and 155.29 ppm in addition to the two alkyne carbons at 101.10 and 88.51 ppm, the methyl carbons of the *t*-Boc unit at 28.55 ppm as well as the methyl groups of the trimethylsilyl moiety at 0.17 ppm.

Another derivative was synthesized by alkylation of 3-trimethylsilylpropargyl iodide with diethyl acetamidomalonate and NaH in anh. DMF at 60 °C. The final dark orange reaction mixture was quenched with 5% aq. NH_4Cl, poured onto water, and extracted with ethyl acetate. Evaporation of the solvent under reduced pressure gave an orange oil which upon purification by column chromatography over silica gel afforded diethyl-α-acetamido-1-trimethylsilyl-α-propargylmalonate as a pale yellow oil in a 61% yield. GC-MS analysis showed only one peak with a m/z of 327, matching with the mass of the expected product. The ^{1}H NMR spectrum showed the amide proton as a singlet at 6.9 ppm, the malonate methylene protons as a multiplet at 4.30-4.17 ppm, the malonate methyl protons at 1.27-1.20 ppm as a triplet, the propargyl protons as a singlet at 3.26 ppm, the methyl protons of the acetamido group as a singlet at 2.04 ppm, and the protons of the trimethylsilyl unit as a large singlet at 0.10 ppm. ^{13}C NMR confirmed the presence of the alkyne carbons recording two signals at 100.80 and 88.34 ppm, and the methylsilyl carbons recording one signal at 0.14 ppm.

The palladium-catalyzed cyclization reaction between 3-(tetrahydro-2-pyranyloxy)-1-(trimethylsilyl)propyne and 3-bromo-2-aminonaphthalene produced a dark brown mixture.

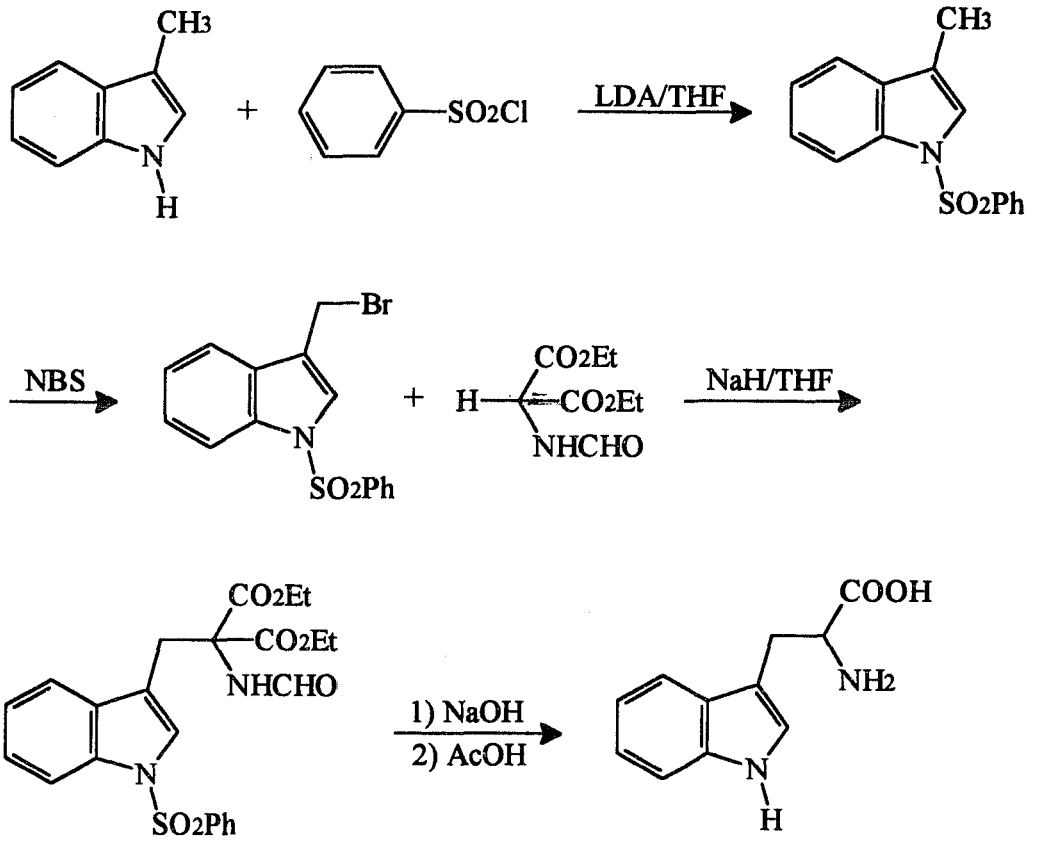
Analysis of the final reaction mixture by GC-MS showed a peak with a m/z of 353, which corresponds to the molecular mass of the expected product. Unfortunately, this benz[*f*]indole derivative was also labile towards column chromatography over silica gel.

In order to find the appropriate reaction conditions to desilylate the benz[*f*]indole intermediates several reported conditions were tested. The crude silylated-alcohol-benz[*f*]indole intermediate obtained when 3-trimethylsilylpropargyl alcohol was concentrated to dryness under reduced pressure, taken up in anh. methanol, and refluxed in the presence of conc. aq. HCl. GC-MS analysis on the final reaction mixture showed that only starting material was present.

A second attempt involved CsF and the silylated intermediate formed between o-iodoaniline and 3-trimethylsilylpropargyl alcohol.[125] GC-MS analysis showed that desilylation did not take place.

The third attempt involved treatment of the silylated-benz[*f*]indole intermediate obtained when using 3-(tetrahydro-2-pyranyloxy)-1-(trimethylsilyl)propyne and $AlCl_3$ in dry DCM at 0 °C.[115] GC-MS analysis on the final reaction mixture revealed the disappearance of starting material; however, several peaks were recorded, and none had the mass of the expected product. This result suggests that, for some unknown reason, the starting material decomposed during the desilylation process.

While exploring methods to desilylate the benz[*f*]indole intermediates another route to synthesize benz[*f*]tryptophan was devised. It is known that 3-methyl-indole reacts with LDA and benzenesulphonylchloride to give N-benzenelsulphonyl-3-methyl-indole which upon treatment with NBS in anh. CCl_4 gives N-benzenesulphonyl-3-bromomethylindole. Alkylation of this 3-substituted indole by a glycine precursor furnishes an intermediate that, after deprotection, gives tryptophan. By following the same reaction sequence, 3-methyl-benz[*f*]indole could be transformed into benz[*f*]tryptophan, Scheme III.23.



Scheme III.23. Synthesis of Trp

Palladium-catalyzed cyclization between 1-trimethylsilylpropyne and 3-bromo-2-aminonaphthalene under the previously established reaction conditions afforded a dark brown mixture. Since this benz[*f*]indole intermediate does not carry any substituent on the methyl group, it was purified easily by column chromatography. TLC over silica gel using a solution of hexanes/ethyl acetate (3:1) to elute the product revealed the absence of starting material and the presence of two compounds, one with an Rf of 0.65 and the other with an Rf of 0.42. The former compound under UV light appeared to have fluorescence

properties (light blue spot) while the latter did not. GC-MS analysis of the compound with an Rf of 0.65 showed only one peak with a m/z of 253, of the expected product. Slow evaporation of the solvents (hexanes/ethyl acetate) afforded yellow crystals with a mp = 116 °C (dec.). Contrary to what was expected, X-ray analysis revealed that those crystals were a racemic mixture of a hydroperoxide derivative of 2-trimethylsilyl-3-methyl-benz[*f*]indole (Figure III.6).

This finding not only suggests that this type of oxidation was the cause of decomposition of the previously described 2-trimethylsilylbenz[*f*]indole intermediates but also that the silylated intermediates must be desilylated immediately after being formed.

In a recent article, Chen and co-workers[116] described the synthesis of several indole derivatives via a palladium-catalyzed coupling reaction between several o-iodoaniline compounds and terminal-silylated 3-butyn-1-ol derivatives under the same reaction conditions previously described. In Chen's study it is reported that desilylation of the isolated 2-silylated indole intermediates was accomplished by reflux in methanol and HCl. Unfortunately, no experimental details were disclosed. In another recent article, Grigg and co-workers reported a series of cycloaddition-palladium catalyzed carbonylation-cyclization reactions involving some 4-iodo-N-benzenesulfonyl-indole derivatives in acetonitrile.[126]

Based on Grigg's study, it was decided to replace anh. DMF by anh. CH_3CN to carry out the palladium-catalyzed cyclization reactions. Also, since it was found that anh. methanol and conc. aq. HCl failed in desilylating the 2-trimethylsilylbenz[*f*]indole intermediates, it was decided to use HCl gas instead.

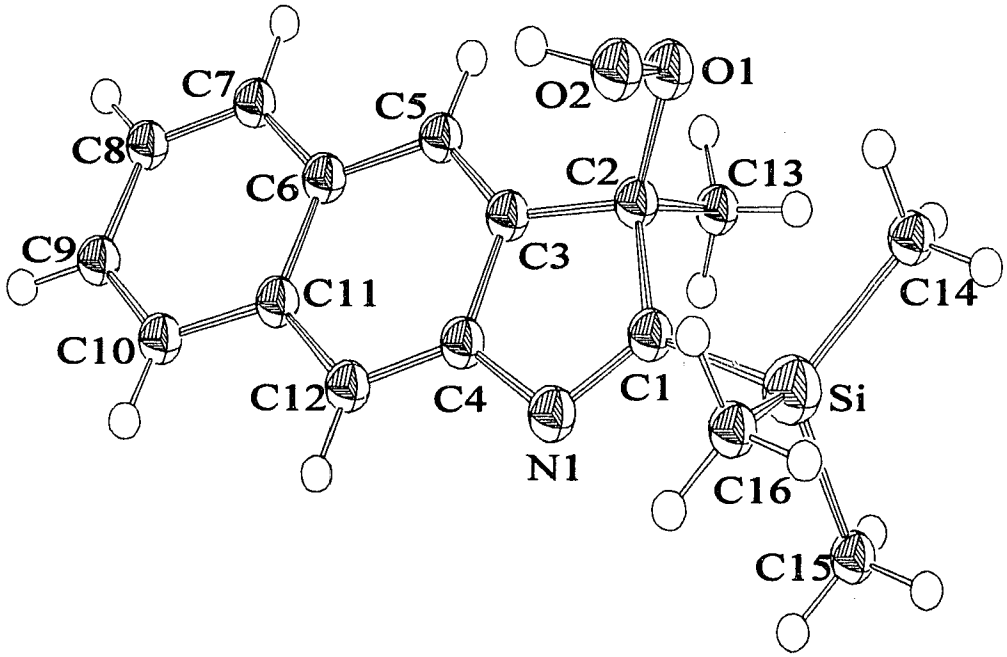


Figure III.6. ORTEP drawing of 2-(trimethylsilyl)-3-methyl-3*H*-benz[*f*]indolyl-3-hydroperoxide

Palladium-catalyzed cyclization reaction of 3-bromo-2-aminonaphthalene and 1-trimethylsilylpropyne in anh. CH_3CN at 100 °C for 4 h gave a dark brown reaction mixture which upon treatment with HCl gas turned immediately to a lighter tone of brown. The reaction mixture was refluxed 1 h, cooled, poured onto aq. NH_4OH, and extracted with ethyl acetate. Usual workup gave a dark brown residue that, upon purification via column chromatography over silica gel, afforded 3-methyl-benz[*f*]indole as a yellow solid with an 81% yield. GC-MS analysis showed only one peak with a m/z of 181, which corresponds to the molecular mass of 3-methyl-benz[*f*]indole. The ^1H NMR spectrum showed the methyl protons as a large sharp singlet at 2.42 ppm integrating for 3 protons. Six well-resolved signals were recorded in the aromatic region, two signals integrated for 2 protons each and the others one proton each, giving a total of 8 protons, the number of protons expected for the benz[*f*]indole framework. ^{13}C NMR shows the methyl carbon at 10.08 ppm and the aromatic carbons between 137.36 ppm and 106.30 ppm.

N-Benzenesulphonyl-3-methyl-benz[*f*]indole was synthesized by reacting crude 3-methyl-benz[*f*]indole with LDA in anh. THF at 0 °C followed by addition of benzenesulphonyl chloride. Evaporation of benzene under reduced pressure left a residue that upon purification by column chromatography over silica afforded a light green solid with a mp = 165 °C (dec.) in a 55% yield. GC-MS recorded only one compound with a m/z of 321, matching the molecular mass of the expected product. The ^1H and ^{13}C NMR spectra showed the methyl protons and carbon appeared practically at the same place as the methyl group of starting material, at 2.32 ppm and 10.06, respectively.

Bromination of this N-protected benz[*f*]indole derivative was carried out using NBS and catalytic benzoylperoxide in anh. benzene under reflux for 3 h to give a dark brown mixture. This mixture was poured onto water, extracted with ethyl acetate, dried over anh. $MgSO_4$, and concentrated under reduced pressure to furnish a dark brown solid. Column

chromatography of this solid over silica gel using a solution of hexanes/DCM (1:1) afforded a light green-brownish solid with a mp = 195 °C in a 38% yield. GC-MS analysis showed the presence of only one compound with a m/z of 401, which is the expected mass of the expected product. The ^{1}H NMR spectrum showed a large singlet at 2.62 ppm which was assumed to belong to the 2 methylene protons. However, the ^{13}C NMR spectrum revealed that the methylene carbon was essentially at the same place as the methyl carbon of the starting material, at 14.22 ppm. This methylene signal was rather suspicious since the halogen atom is expected to have a deshielding effect on the methylene carbon, whose net effect would be the shifting of the methylene carbon to a region downfield, perhaps between the 25 and 40 ppm. The light green-brownish solid was recrystallized from hot ethyl acetate to give light purple crystals with a mp = 200 °C. X-ray analysis on these crystals revealed that the bromination had taken place unexpectedly on the anthracene-like aromatic carbon of the benz[*f*]indole framework to afford N-benzenesulfonyl-4-bromo-3-methyl-benz[*f*]indole (Figure III.7), Scheme III.24.

This finding does not agree with recent bromination studies on 3-methylindole derivatives with N-bromosuccinimide. Zhang[127] and co-workers have recently reported that the bromination site on 3-methylindoles clearly depends on the substituents on the indole ring. It is demonstrated that the benzenesulfonyl group, an electron withdrawing group, at the N position affords exclusively bromination on the methyl group on position 3 with good yields. On the other hand, when the N site does not bear any substituent the bromination takes place exclusively on C(2) with good yields. Interestingly, Zhang noticed that N-benzenesulfonyl-3-methylindole undergoes bromination on the methyl group under both free radical and electrophilic conditions essentially with the same yields (92-94%).[127]

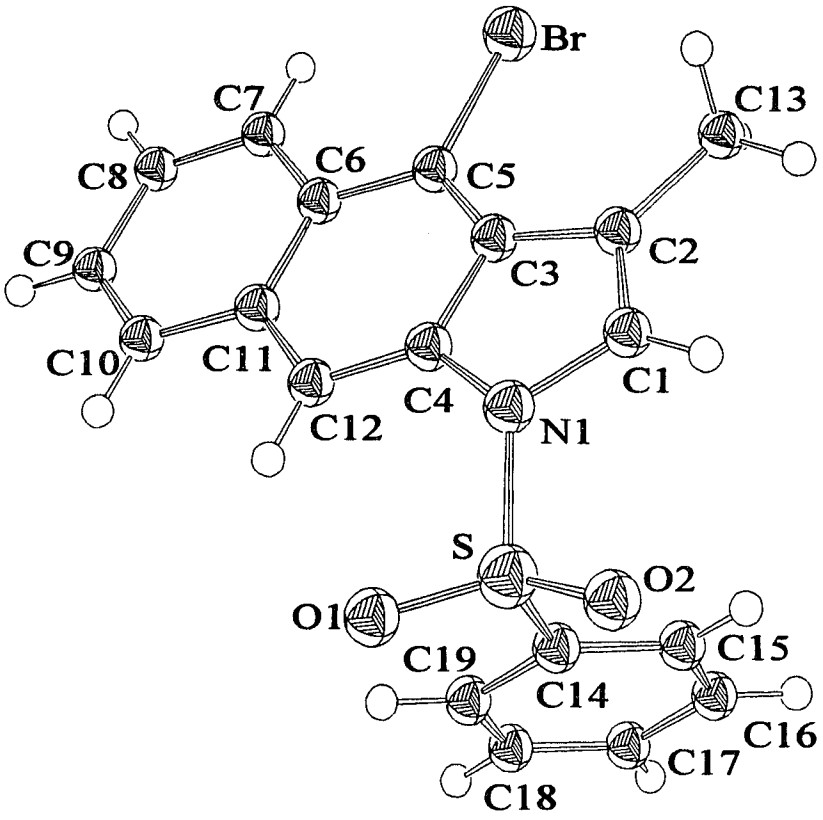
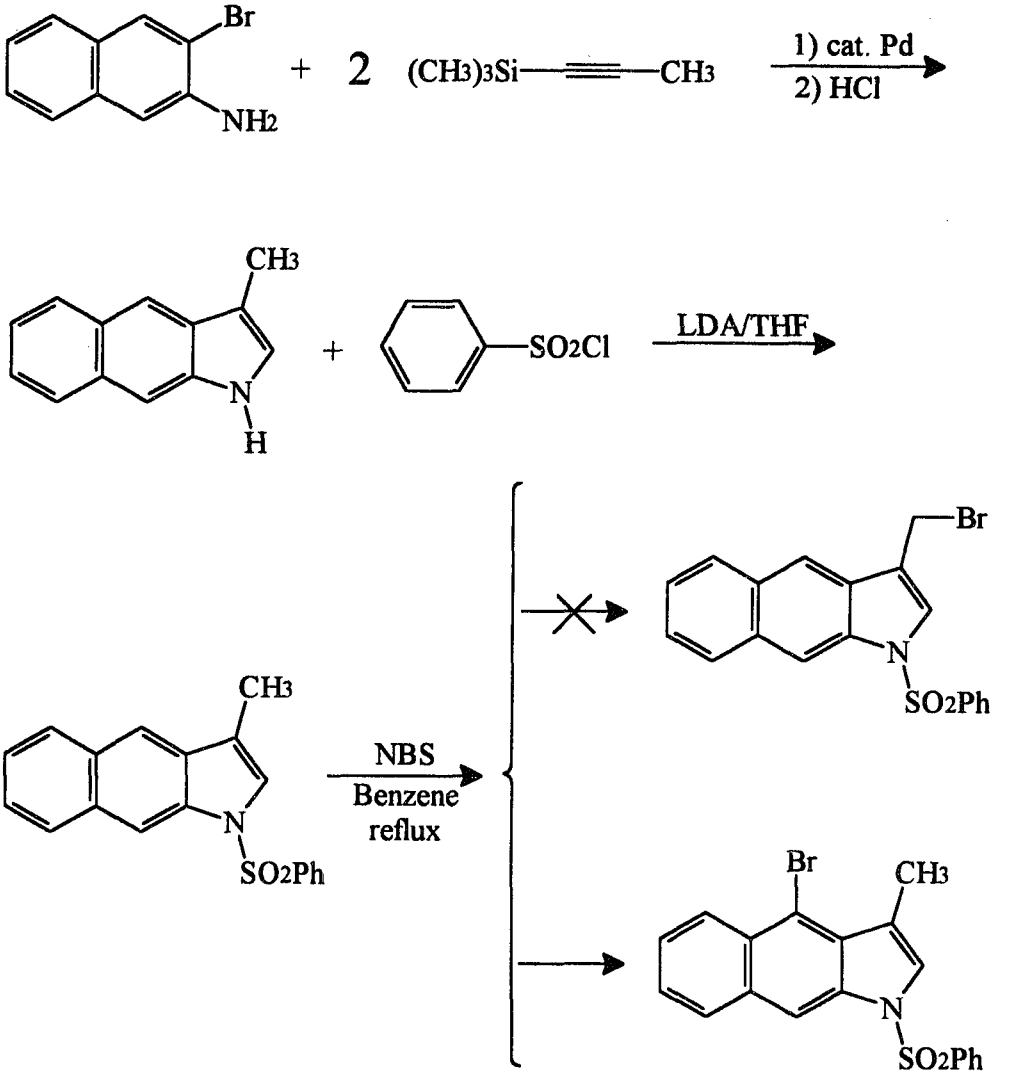


Figure III.7. ORTEP drawing of N-benzenesulfonyl-4-bromo-3-methyl-benz[*f*]indole



Scheme III.24. Attempted synthesis of N-benzenesulfonyl-3-(bromomethyl)benz[*f*]indole

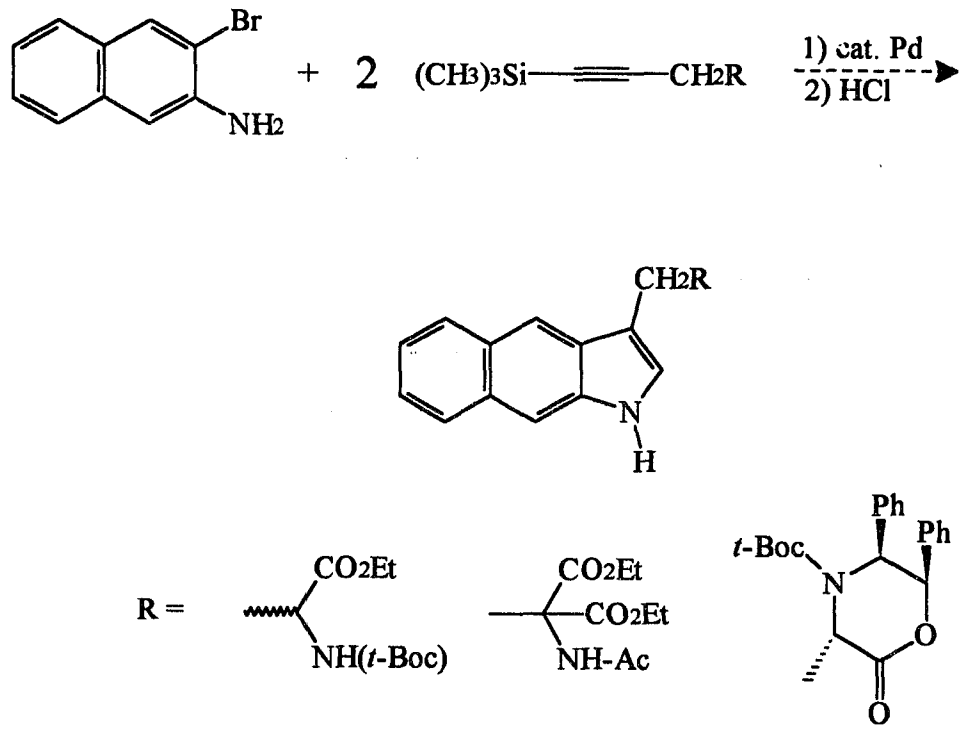
In order to use this derivative to accomplish the synthesis of benz[*f*]tryptophan, still having to remove eventually the aromatic bromide, another bromination reaction was attempted between N-benzenesulfonyl-4-bromo-3-methyl-benz[*f*]indole and NBS with

catalytic benzoylperoxide in anh. benzene under reflux for 3 h. GC-MS analysis on the final reaction mixture revealed only the presence of starting material. The methyl unit of this benz[*f*]indole derivative is unreactive towards a second bromination.

The palladium-catalyzed reaction between the alkylated William's template and 3-bromo-2-aminonaphthalene under the latest reaction conditions produced a dark brownish gooey residue which was triturated in deionized water. The aqueous solution was separated, its pH was adjusted to 7 with aq. 1N NH_4OH, and then it was freeze-dried under high vacuum to afford an orange solid residue. Although its ^1H NMR spectrum had signals in the aromatic and aliphatic areas, these signals did not provide enough information to elucidate if the desired molecule had been obtained or not.

In order to avoid this ^1H NMR-spectrum elucidation problem, 3-bromo-2-aminonaphthalene was reacted with ethyl N-(*t*-Boc)-4(trimethylsilyl)4-pentynoate under the above reaction conditions. As in the alkylated William's template reaction, a dark orange-brownish gooey residue was obtained. The same workup was followed by purification over acidic ion-exchange column which afforded an orange-brownish solid whose ^1H NMR spectrum did not present any signals in the aromatic region.

Palladium-catalyzed cyclization reaction between diethyl-α-acetamido-1-trimethylsilyl-α-propargylmalonate and 3-bromo-2-aminonaphthalene afforded at the end, as in the two previous glycine-precursor-containing 3-trimethylsilylpropargyl-derivatives cyclization reactions, an orange gooey material. Attempts to purify this product by column chromatography over silica gel succeeded in separating starting materials from the orange material; however, the high affinity of this orange material to silica gel made its separation impossible from other unknown substances. The ^1H NMR spectrum recorded signals in the aromatic region and the aliphatic area; however, other unidentified signals in the 5.00-4.00 ppm region were also recorded, Scheme III.25.



Scheme III.25. Attempted Pd-catalyzed cyclizations with glycine-precursor-containing terminal-silylated alkynes

The last attempts to synthesize benz[f]tryptophan involved the sinthesis of 4-trimethylsilyl-3-butynal diethoxy acetaldehyde and 4-trimethylsilyl-3-butyn-1-oxy-trimethylsilane, two terminal-silated alkyne derivatives containing functional groups that, upon further chemical transformations, would provide the α-amino acid moiety. However, these alkyne derivatives also failed in providing the expected benz[*f*]indole intermediates.

CHAPTER IV. EXPERIMENTAL SECTION

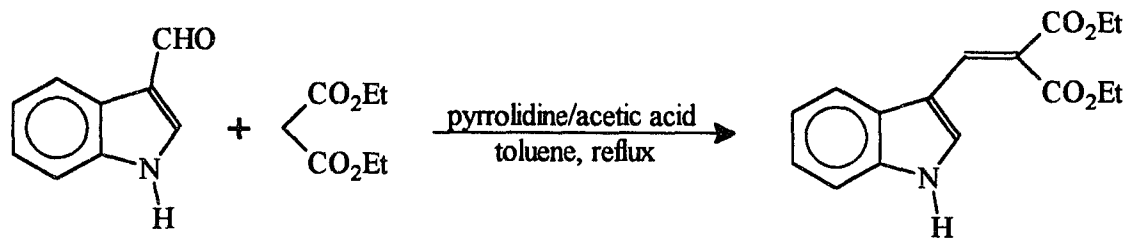
IV.1. Technical information.

All chemicals were used without further purification, unless indicated otherwise. Benzene, DMF, Et_3N, and DMSO were pre-dried, distilled and stored under argon. Hexanes and DCM were refluxed and distilled from CaH_2, diethyl ether from a Na/K alloy, and THF from K. Silica gel used in column chromatography was 60-200 Å mesh.

NMR spectra were recorded on Bruker spectrometers at 200 MHz for ^1H (50 MHz for ^{13}C), 250 MHz (62.5 MHz for ^{13}C), and 300 MHz (75 MHz for ^{13}C). Coupling constants are reported in Hertz. Chemical shifts are reported in δ or ppm relative to internal-standard tetramethylsilane (TMS).

GC/MS spectra (electron impact) were recorded on a Hewlett-Packard 5971 mass spectrometer operated at 70 eV.

IV.2. Procedures.

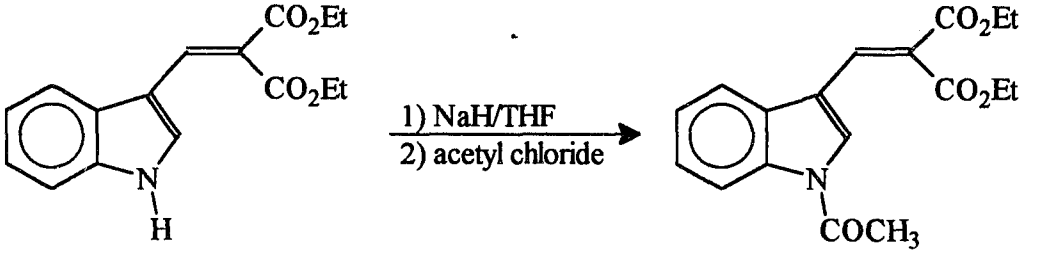


IV.2.1. Ethyl 2-carbomethoxy-3-(3-indolyl)acrylate. In a 500-mL one-necked round-bottomed flask fitted with a Dean-Stark trap, a condenser and a drierite drying tube, indole-3-carboxaldehyde (29.0 g, 0.20 mol), diethyl malonate (48.0 g, 0.30 mol), toluene (200 mL), pyrrolidine (2.0 mL) and glacial acetic acid (2.0 mL) were mixed. The solution was refluxed under stirring until the theoretical amount of water was removed. The final

reaction mixture was concentrated under reduced pressure. The residue was dissolved in ether, washed with a 5% aq. solution of HCl (100 mL) and a 5% aq. solution of sodium bicarbonate (100 mL), dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure. The resulting solid was recrystallized once from hot ethanol to afford yellow crystals (30.36 g, 52.89% yield); mp = 90-92 °C.

^1H NMR($CDCl_3$ + TMS) (250 MHz): δ 9.21 (broad s, 1H), 8.12 (s, 1H), 7.75-7.70 (m, 2H), 7.40-7.33 (m, 1H), 7.27-7.18 (m, 2H), 4.37-4.27 (m, 4H), 1.37-1.24 (m, 6H).

^{13}C NMR ($CDCl_3$ + TMS) (62.5 MHz): δ 168.12, 165.40, 135.77, 135.07, 127.83, 127.46, 123.21, 121.40, 119.54, 118.40, 111.72, 110.36, 61.47, 61.17, 14.20, 13.98



IV.2.2. Diethyl 2-(N-acetyl-indolyl-3-methylene)malonate. In a 250-mL three-necked round-bottomed flask equipped with a thermometer, a glass stopper, an addition funnel, a bubbler, and a magnetic stirring bar, sodium hydride (60% dispersed in oil) (1.12 g, 28.0 mmol) was washed with dry hexanes (3 x 30 mL) under argon to remove the mineral oil. Argon was flowed through the system for about 5 min until the sodium hydride was dry, then dry THF (50 mL) was added. The flask was placed in an ice-water bath under stirring to reach 4 °C.

In a separate flask, diethyl 2-(indolylmethylene)malonate (5.74 g, 20.0 mmol) was dissolved in dry THF (40 mL). This solution was transferred to an addition funnel. Argon was flowed again for 1 min through the system. This solution was added dropwise into the THF/NaH suspension under stirring keeping the temperature of the reaction mixture below 5 °C.

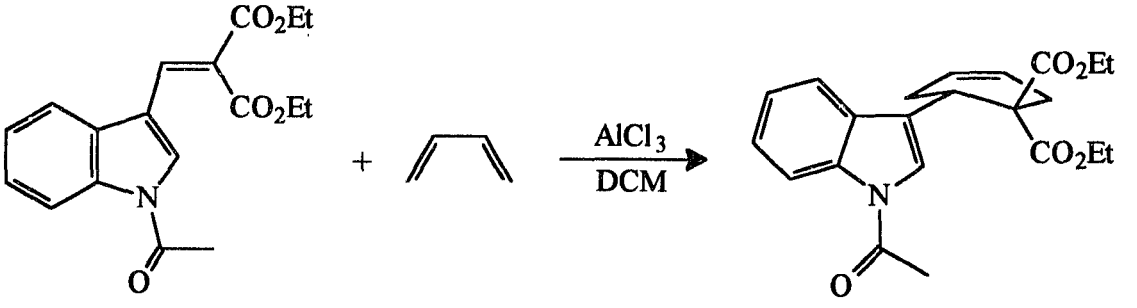
After complete addition of the THF/2-(indolylmethylene)malonate solution, acetyl chloride (2.55g, 25 mmol) in dry THF (20 mL) was transferred to the addition funnel and added dropwise under stirring keeping the temperature of the reaction mixture below 5 °C.

The reaction mixture was stirred for one h at 4 °C, the ice-water bath was removed, and the reaction mixture was allowed to reach room temperature and stirred overnight. The final light-greenish reaction mixture was poured onto 200 mL of water and the product extracted with ethyl ether (3 x 70 mL). The etheral extracts were combined, dried over anh. $MgSO_4$, and concentrated to afford a yellow solid. The solid residue was purified by flash chromatography on a silica gel column (hexanes-ethyl acetate, 2:1) to give a white solid (5.17 g, 78.6% yield); mp = 88-89 °C.

^1H NMR ($CDCl_3$ + TMS) (250 MHz): δ 8.46-8.41 (dd, 1H), 7.97-7.95 (d, 2H), 7.73-7.68 (dd, 1H), 7.46-7.32 (m, 2H), 4.41-4.29 (m, 2H), 2.66 (s, 3H), 1.40-1.30 (m, 3H).

^{13}C NMR ($CDCl_3$ + TMS) (62.5 MHz): δ 168.55, 165.86, 164.28, 135.43, 132.50, 129.51, 126.87, 126.10, 125.33, 124.37, 118.55, 116.73, 115.41, 114.52, 61.78, 61.60, 23.86, 14.19, 14.01

GC-MS (m/z): 329, 287, 242, 215, 196, 169, 141, 115, 43



IV.2.3. Diethyl 6-(N-acetyl-3-indolyl)cyclohex-3-ene-1,1-dicarboxylate. In a 100-mL three-necked round-bottomed flask equipped with a magnetic stirring bar, an oil bubbler, a low-temperature thermometer, and an argon inlet, $AlCl_3$ (2.0 g, 14.9 mmol) was mixed with DCM (20 mL) with stirring under an argon atmosphere. This suspension was placed in a dry ice-acetone bath. When the temperature was below -50 °C, diethyl 2-(N-acetyl-indolyl-3-methylene)malonate (0.987 g, 3.00 mmol) dissolved in DCM (10 mL) was added via syringe under stirring. The reaction mixture was cooled to -70 °C, and an excess of 1,3-butadiene was flowed gently into the flask for 30 min. The dry ice-acetone bath was then removed allowing the reaction reach 0 °C, then an ice-water bath was used to keep the temperature at 5 °C. 1,3-Butadiene was flowed again into the reaction flask for another 30 min. The temperature was kept at 4 °C for 2 h, then the ice-water bath was removed and the reaction mixture was stirred at room temperature overnight.

The final reaction mixture was poured onto a 5% aq. solution of $NaHCO_3$ (200 mL) under vigorous stirring. The organic phase was separated and the aqueous phase extracted with DCM (2 x 100 mL). The organic extracts were combined, dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure to afford an orange oil (1.58 g). This oily residue was chromatographed on silica gel using hexanes/ethyl acetate (4:1) to obtain a yellow oil. Crystallization from hot hexanes afforded white crystals (0.081 g, 20.88%

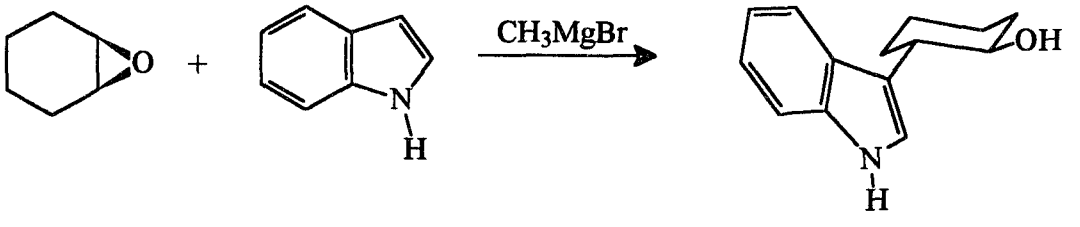
yield); mp = 98-99 °C. X-ray crystallography confirms the formation of the desired product.

^{1}H NMR ($CDCl_3$ + TMS) (200 MHz): δ 8.41-8.37 (d, 1H), 7.56-7.48 (m, 2H), 7.35-7.20 (m, 2H), 5.83 (s, 2H), 4.10-3.80 (m, 5H), 2.9 (s, 2H), 2.6 (s, 2H), 1.26-1.04 (t, 6H).

^{13}C NMR ($CDCl_3$ + TMS) (50 MHz): δ 170.88, 170.05, 168.50, 134.99, 130.57, 126.76, 125.10, 123.89, 123.57, 123.16, 118.75, 116.44, 61.52, 61.26, 56.16, 33.13, 31.02, 29.05, 24.04, 13.77, 13.72

GC-MS (m/z): 383, 338, 287, 267, 238, 222, 194, 168, 159, 143, 130, 117, 43

IR (cm^{-1}): 2981, 1732, 1708, 1452, 1381, 1333, 1246, 1180, 1060, 1016, 751, 658



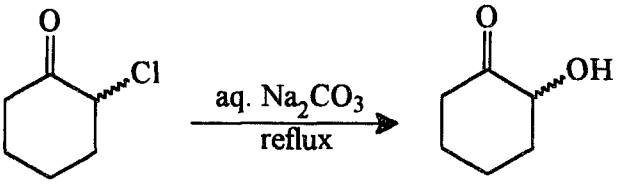
IV.2.4. *trans*-3-(2-Hydroxycyclohexyl)indole. This compound was prepared according to the procedure reported by Ghosh.[128] To a well-stirred solution of indole (10.0 g, 85.4 mmol) in ethyl ether (30 mL) a solution of methylmagnesium bromide (87 mmol) was added dropwise under an argon atmosphere. The rate of the addition was adjusted to mantain a gentle reflux. The mixture was then stirred for 45 min at room temperature. A solution of cyclohexene oxide (8.5 g, 86.7 mmol) in ethyl ether (10 mL) was added dropwise. The resulting suspension was stirred overnight. The final reaction mixture was quenched with slow addition of saturated aqueous solution of $NaHCO_3$ (100 mL) and

filtered. The white solid was washed repeatedly with ethyl acetate (4 x 50 mL). The combined organic layers were dried over anh. $MgSO_4$ and concentrated under reduced pressure to leave a yellowish white solid. Recrystallization from hexanes/ethyl acetate (10:1) afforded a light pinkish solid (7.5 g, 40.8% yield); mp = 158-159 °C.

^1H NMR ($CDCl_3$ + TMS) (250 MHz): δ 8.16 (br s, 1H), 7.74-7.71 (d, 1H), 7.37-7.34 (d, 1H), 7.25-7.11 (m, 2H), 7.08 (d, 1H), 3.82-3.73 (td, 1H), 2.80-2.72 (td, 1H), 2.18-1.38 (m, 8).

^{13}C NMR ($CDCl_3$ + TMS) (62.5 MHz): δ 136.61, 127.07, 122.21, 121.28, 119.55, 119.42, 117.70, 111.27, 74.73, 44.51, 34.27, 32.64, 26.27, 25.08

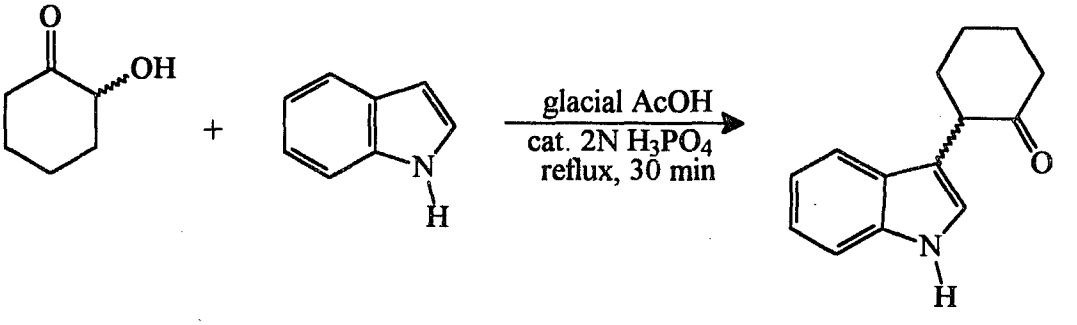
GC-MS (m/z): 215, 198, 156, 143, 130, 115, 103, 77



IV.2.5. 2-Hydroxy-cyclohexanone. This compound was prepared according to the procedure reported by Hiroyuki.[129] In a 100-mL one-necked round-bottomed flask equipped with a magnetic stirring bar and a condenser Na_2CO_3 (3.18 g, 30.0 mmol) was dissolved in water (40 mL). To this solution, 2-chlorocyclohexanone (6.63 g, 50.0 mmol) was added and the reaction mixture was refluxed with stirring for 1 h. The final light yellow solution was cooled in a refrigerator for 24 h to afford a white precipitate. The white solid was filtered, washed with small portions of acetone, and dried under high vacuum to afford a white solid (dimer) (3.91 g, 62.1% yield); mp = 120-124 °C.

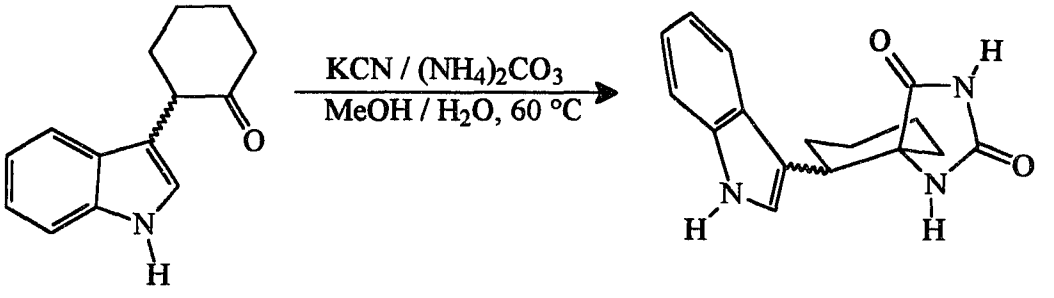
^{1}H NMR (DMSO-d_6 + TMS) (250 MHz): δ 5.52 (s, 1H), 3.89 (d, 1H), 1.65-1.23 (m, 8H).

^{13}C NMR (DMSO-d_6 + TMS) (62.5 MHz): δ 94.31, 72.15, 35.36, 27.57, 24.10, 22.19



IV.2.6. 2-(3-Indolyl)cyclohexanone. This compound was prepared according to the procedure reported by Freter.[130] A mixture of indole (0.585 g, 5.0 mmol), 2-hydroxycyclohexanone (1.89, 7.50 mmol), glacial acetic acid (5 mL) and 2N H_3PO_4 (1 mL) was refluxed at 135-140 °C for 30 min. The final red-orange mixture was cooled using an ice-water bath, then poured onto ice-cold concentrated NH_4OH (20 mL) under vigorous stirring to form a yellow solid. This yellow solid was extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with water (3 x 10 mL), aqueous 5% NH_4Cl (1 x 20 mL), dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure. The orange gooey residue was taken up in a minimum volume of DCM and chromatographed over silica gel using DCM as the eluent to obtain a light brown solid (0.31 g, 28.92% yield).

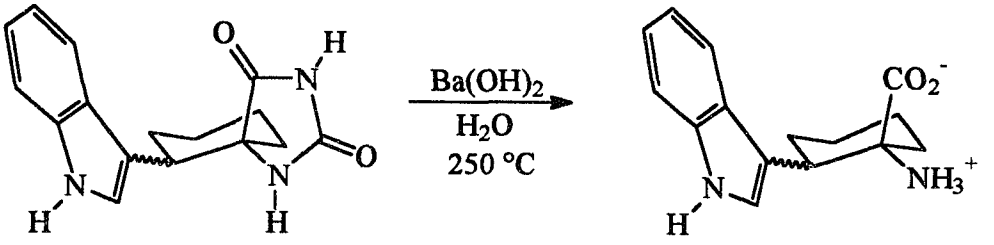
^{1}H NMR ($CDCl_3$ + TMS) (250 MHz): δ 8.23 (br s, 1H), 7.44-7.42 (d, 1H), 7.24-7.21 (d, 1H), 7.16-7.03 (m, 2H), 6.89 (d, 1H), 3.92-3.85(m, 1H), 2.55-247 (m, 1H), 2.31-1.27 (m, 9H).



IV.2.7. 2-(3-Indolyl)cyclohexanespiro-5'-hydantoin. In a 25-mL one-necked round-bottomed flask equipped with a septum, an oil bubbler, and a magnetic stirring bar, 2-(3-indolyl)cyclohexanone (0.483 g, 2.26 mmol) was dissolved in warm methanol (5 mL). To this mixture KCN (0.434 g, 6.67 mmol), $(NH_4)_2CO_3$ (0.32 g, 3.33 mmol) in water (5 mL) were added. The reaction flask was immersed in a pre-heated oil bath (60 °C) and the reaction mixture was stirred for 12 h. The final reaction mixture was poured into water (50 mL) and stirred during 1 h. The precipitate is filtered under suction, the filtrate was concentrated under reduced pressure to give more solid. The combined solids were dried under high vaccum to give a light cream solid (0.514 g, 80.4% yield); mp = 159-160 °C (dec.)

^{1}H NMR (DMSO-d_6 + TMS) (250 MHz): δ 10.88 (s, H-N), 9.99 (s, -CO-NH-CO-, 1H), 8.50 (s, -C-NH-CO-, 1H), 7.53-7.50 (d, 1H), 7.28-7.25 (d, 1H), 7.09-7.08 (d, 1H), 7.02-6.97 (t, 1H), 6.93-6.87 (t, 1H), 3.36-3.20 (dd, 1H), 1.99-1.42 (m, 8H).

^{13}C NMR (DMSO-d_6 + TMS) (62.5 MHz): δ 177.72, 156.92, 135.33, 126.66, 122.84, 120.59, 118.89, 118.02, 113.78, 110.98, 66.11, 38.71, 34.22, 29.39, 25.70, 20.71

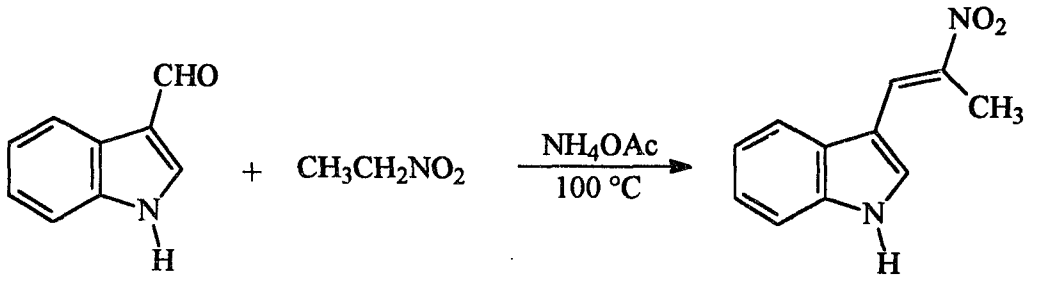


IV.2.8. 1-Amino-2-(3-indolyl)-cyclohexane-1-carboxylic acid. In a Parr® high pressure bomb, 2-(3-indolyl)cyclohexanespiro-5'-hydantoin (50 mg, 1.7667 x 10^{-4} mol) and $Ba(OH)_2 \cdot H_2O$ (0.1338 g, 6.463 x 10^{-4} mol) were suspended in oxygen-free water (50 mL) in an argon atmosphere (40 psi). The bomb was placed in a sand bath at 250 °C for 24 h. After cooling the bomb with an ice-water bath the resulting solution was filtered and its pH adjusted to 7 with 1N HCl. The solution was then freeze-dried under high vacuum. The resulting residue was taken up in the minimum amount of deionized water and desalted by ion-exchange column. The collected fractions were freeze-dried to afford a cream colored solid (0.0125 g, 27.4% yield); mp = 207-209 °C(dec.)

^{1}H NMR (DMSO-d_6 + TMS) (300 MHz): δ 10.86 (br s, N-H), 7.72-7.29(d, 1H), 7.27-7.24 (d, 1H), 7.14 (d, 1H), 7.01-6.96 (t, 1H), 6.33-6.84 (t, 1H), 3.54-3.49 (dd, 1H), 2.12-1.90 (m, 2H), 1.83-.1.76 (t, 2H), 1.65-1.52 (d, 2H), 1.49-1.38 (t, 2H).

^{13}C NMR (DMSO-d_6 + TMS) (75 MHz): δ 173.53, 136.57, 128.09, 123.86, 121.46, 121.15, 118.74, 115.64, 111.48, 63.89, 39.04, 34.52, 29.46, 26.92, 21.56

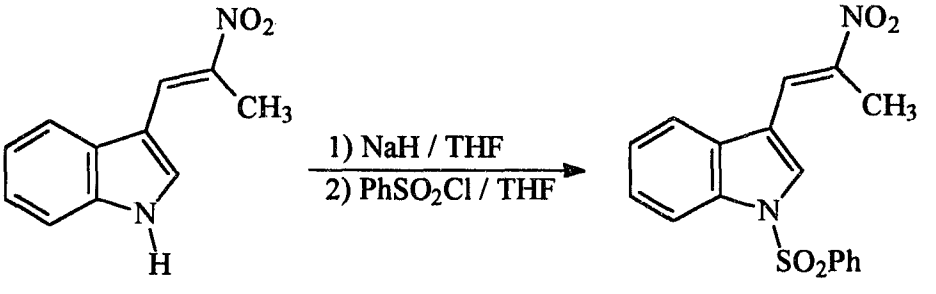
FAB: 259.1, 242



IV.2.9. 3-2'-Methyl-2'-nitro-vinylindole. This compound was prepared according to the procedure reported by Kusurkar.[131] Indole-3-carboxaldehyde (97%) (15.0 g, 0.1032 moles), nitroethane (41.76 g, 0.5568 moles) and ammonium acetate (3.00 g, 0.039 moles) were heated at 100 °C for 3 h in an argon atmosphere with magnetic stirring. The final dark brown mixture was cooled by using an ice-water bath to afford a dark brown solid. This solid was washed with hot water (80 °C) (4 x 50 mL) and recrystallized from 95% ethanol to give a dark brown-orange solid (13.7 g, 65.5% yield); mp = 192-194 °C.

^{1}H NMR (DMSO-d_6 + TMS) (250 MHz): δ 12.24 (br s, N-H), 8.48 (s, 1H), 8.02 (s, 1H), 7.86-7.83 (d, 1H), 7.54-7.51 (d, 1H), 7.30-7.18 (m, 2H), 3.1 (s, 3H).

GC-MS (m/z): 202, 185, 169, 154, 145, 128, 117, 104, 89, 77 63, 51



IV.2.10. N-(Benzenesulfonyl)-3-(2'-methyl-2'-nitro)-vinylindole. A 100-mL three-necked round-bottomed flask fitted with a thermometer, a glass stopper, an addition

funnel, an oil bubbler, and a magnetic stirring bar, was charged with sodium hydride (60% dispersed in oil) (0.32 g, 8.0 mmol). The sodium hydride was washed with anh. hexanes (2 x 10 mL) under argon to remove the mineral oil. Argon was flowed through the system for about 5 min until the sodium hydride was dry, then dry THF (20 mL) was added. The flask was placed in an ice-water bath under stirring to reach 4 °C.

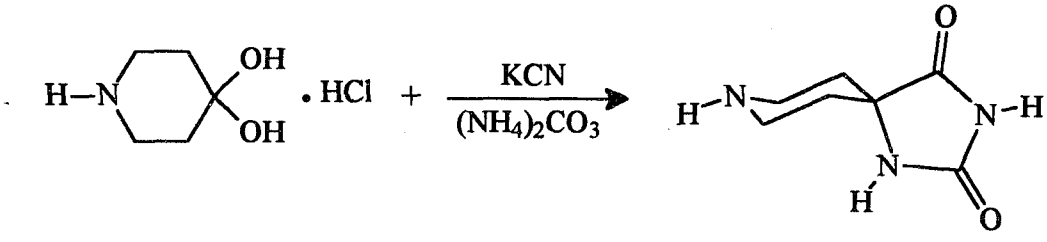
In a separate flask 3-2'-methyl-2'-nitro-vinylindole (1.01 g, 5.0 mmol) was dissolved in anh. THF (20 mL). This solution was transferred into the addition funnel. Argon was flowed again for 1 min through the system. This solution was added dropwise into the THF/NaH solution under stirring keeping the temperature of the reaction mixture below 5 °C.

Once the entire THF/indole solution was added a solution of benzenesulphonyl chloride (1.06 g, 6.0 mmol) in anh. THF (10 mL) was transfered into the addition funnel. This solution was added dropwise under stirring keeping the temperature of the reaction mixture below 5 °C.

The reaction mixture was stirred for 1 h at 4 °C, the ice-water bath was removed, and the reaction mixture was allowed to reach room temperature. The reaction mixture was stirred overnight. The final light-greenish reaction mixture was poured onto 5% aq. HCl (100 mL) under vigorous stirring, transferred to a separatory funnel and extracted with DCM (4 x 50 mL), dried over anh. $MgSO_4$, and concentrated under reduced pressure. The resulting solid residue was purified through column chromatography over silica gel using a solution of hexanes/DCM (1:1) to afford a light green colored solid (0.43 g, 40% yield); m.p. = 182-183 °C.

^{1}H NMR ($CDCl_3$ + TMS) (200 MHz): δ 8.22 (s, 1H), 8.04-8.00 (d, 1H), 7.75-7.92 (d, 1H), 7.84-7.81 (d, 1H), 7.77-7.67 (d, 1H), 7.64-7.28 (m, 6H), 2.55 (s, 3H).

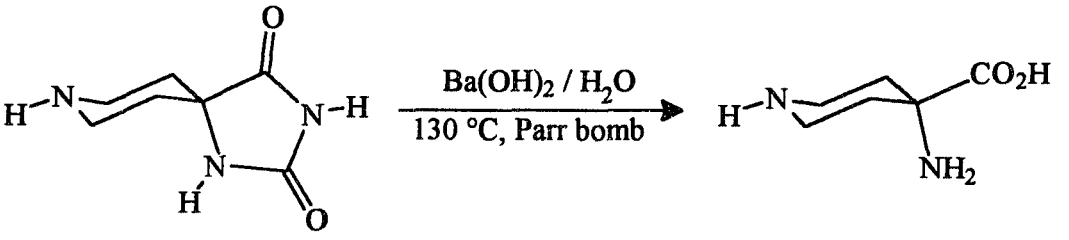
^{13}C NMR ($CDCl_3$ + TMS) (50 MHz): δ 137.91, 134.67, 130.02, 129.81, 127.15, 126.84, 126.30, 124.48, 123.44, 119.69, 113.93, 15.16



IV.2.11. 4-Piperidinespiro-5'-hydantoin. In a 200-mL one-necked round-bottomed flask equipped with a magnetic stirring bar, 4-piperidone monohydrate hydrochloride (6.822 g, 44.41 mmol), water (90 mL), conc. NH_4OH (24 mL, 360 mmol) and MeOH (9.0 mL, 219 mmol) were mixed and stirred until the piperidone derivative was completely dissolved. To this solution, $(NH_4)_2CO_3$ (36.0 g, 375 mmol) and KCN (9.0g, 138 mmol) were added to the reaction flask. The reaction mixture was stirred at room temperature for 12 h. The final white suspension was filtered off, washed with water (2 x 10 mL), and dried under high vacuum to give a white solid (6.14 g, 81.8% yield), mp = 320-330 °C (dec.)

^1H NMR (DMSO-d_6 + TMS) (250 MHz): δ 10.50 (b s, 1H), 8.47 (s, 1H), 2.88-2.79 (dt, 1H), 2.72-2.62 (dt, 1H), 1.74-1.62 (dt, 1H), 1.40-1.34 (d, 1H).

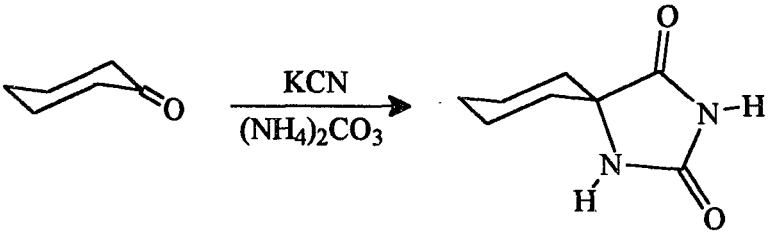
^{13}C NMR (DMSO-d_6 + TMS) (62.5 MHz): δ 177.93, 156.22, 60.94, 41.10, 33.74.



IV.2.12. 4-Amino-piperidine-4-carboxylic acid. In a Parr® high pressure bomb 4-piperidinespiro-5'-hydantoin (0.338 g, 2.00 mmol) and $Ba(OH)_2 \cdot H_2O$ (1.04 g, 5.5 mmol) were suspended in water (25 mL). The bomb was placed in a sand bath at 130 °C for 8 h. After cooling the bomb, excess of $(NH_4)_2CO_3$ was added and the mixture was heated at 80 °C for 30 min. The mixture was cooled overnight, filtered and freeze-dried to afford a white solid (0.188 g, 65.4% yield); mp = 276-278 °C (dec.).

^1H NMR (D_2O + TSP) (200 MHz): δ 3.47-3.29 (m, 1H), 3.24-3.00 (m, 1H), 2.25-1.77 (m,2H).

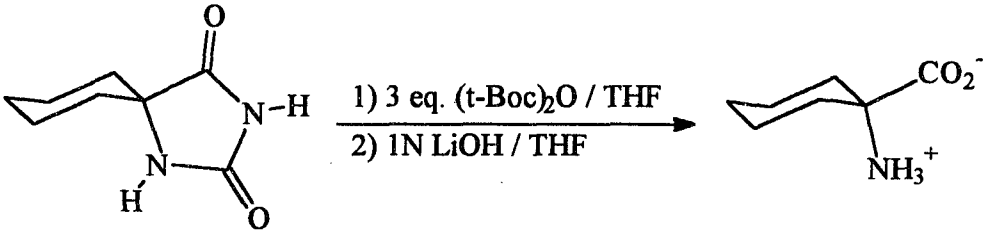
^{13}C NMR (D_2O + TSP) (50 MHz): δ 182.36, 59.10, 42.72, 32.12



IV.2.13. Cyclohexanespiro-5'-hydantoin. This compound was prepared according to the procedure reported by Tsang.[132] In a 100-mL one-necked round-bottomed flask equipped with a magnetic stirring bar, KCN (2.6 g, 40.0 mmol) and $(NH_4)_2CO_3$ (3.84 g, 40.0 mmol) were mixed and dissolved in water (10 mL). Cyclohexanone (1.96 g, 20.0

mmol) was added followed by methanol (50 mL) under stirring. The reaction mixture was stirred overnight at room temperature. The final white suspension was cooled in a refrigerator for 24 h and the resulting white precipitate was filtered and dried under high vacuum (2.7 g, 80 % yield); mp = 216-217 °C.

^{1}H NMR (DMSO-d_6 + TMS) (200 MHz): δ 10.45 (b s, 1H), 8.37 (s, 1H), 1.58-1.16 (m, 10H).



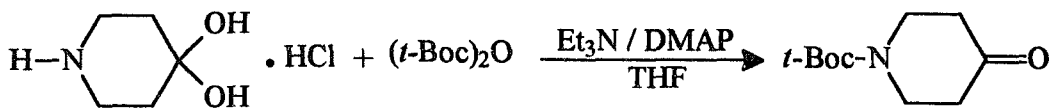
IV.2.14. 1-Amino-cyclohexane-1-carboxylic acid. In a 25-mL one-necked round-bottomed flask equipped with a magnetic stirring bar, cyclohexanespiro-5'-hydantoin (0.168 g, 1.0 mmol) and di-*tert*-butyl dicarbonate (0.66 g, 3.0 mmol) were mixed in dry THF (15 mL) under stirring at room temperature. To this suspension, a catalytic amount of DMAP was added. The mixture became homogeneous within the first 5 min of stirring. One h later, the final mixture was filtered through a silica pad and the pad was washed with THF (80 mL). The filtrate was then concentrated under reduced pressure to afford a cream colored solid (0.37 g, 100% yield); mp = 151-152 °C.

This solid was transferred to a 250-mL one-necked round-bottomed flask equipped with a magnetic stirring bar and suspended in THF (100 mL). To this suspension, aq. 1N LiOH (8 mL, 8.0 mmol) was added and the mixture was stirred at room temperature for 4 h. The final reaction mixture was concentrated under reduced pressure, the pH adjusted to

7, and freeze-dried. The residue was purified by ion-exchange and freeze-dried to afford a white solid (0.078 g, 54% yield); mp = 300 °C< (dec.)

^{1}H NMR (D_2O + TSP) (200 MHz): δ 2.02-1.92 (m, 1H), 1.77-1.71 (d, 2H), 1.55-1.44 (m,1H).

^{13}C NMR (D_2O + TSP) (50 MHz): δ 181.49, 64.17, 34.77, 27.04, 23.46



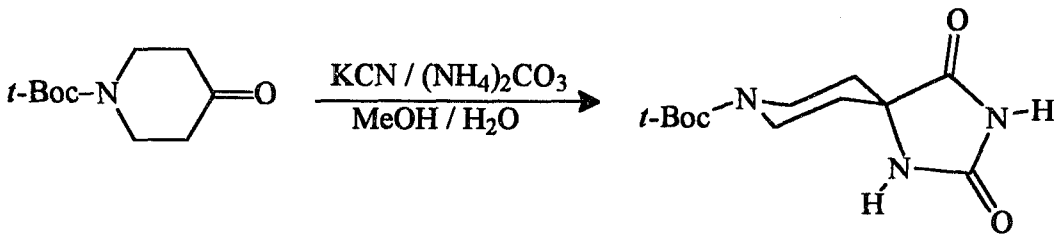
IV.2.15. N-(*t*-Boc)-4-piperidinone. In a 100-mL one-necked round-bottomed flask, 4-piperidinone monohydrate hydrochloride (1.536 g, 10.0 mmol) was suspended in dry THF (40 mL). To this suspension, triethylamine (1.515 g, 15.0 mmol) was added under vigorous stirring. After stirring for 5 min, di-*tert*-butyl carbonate (2.619 g, 12.0 mmol) was added all at once followed by a catalytic amount of DMAP. After stirring for 12 h at room temperature, the final reaction mixture was concentrated under reduced pressure. The residue was taken up in DCM (50 mL), washed with 2N aq. HCl (2 x 35 mL), sat. aq. Na_2CO_3 (1 x 25 mL), brine (1 x 25 mL), dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure to give a light brownish solid (1.50 g, 75.5 % yield); mp = 63-64 °C.

^{1}H NMR ($CDCl_3$ + TMS) (250 MHz): δ 3.72 (t, 2H), 2.44 (t, 2H), 1.49 (s, 9H).

^{13}C NMR ($CDCl_3$ + TMS) (62.5 MHz): δ 207.69, 154.53, 80.43, 43.08, 41.20, 28.43

GC-MS (m/z): 199,184, 144, 126, 115, 98, 70, 57

IR (cm^{-1}): 2980, 2360, 2341, 1688, 1246, 1361, 1247, 1169, 984, 669

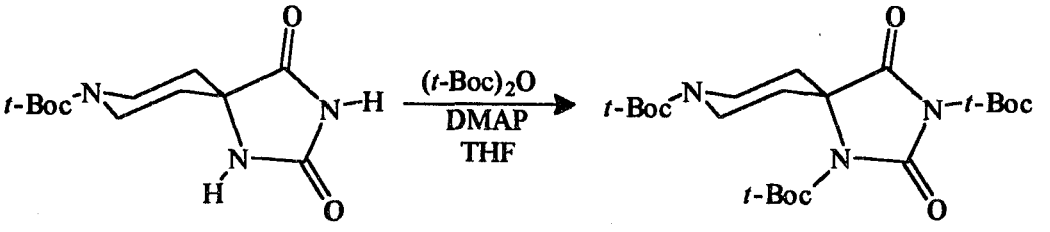


IV.2.16. N-(*t*-Boc)-4-piperidinespiro-5'-hydantoin. In a 100-mL one-necked round-bottomed flask equipped with a magnetic stirring bar, KCN (6.21 g, 95.58 mmol) and NH_4CO_3 (9.17 g, 95.58 mmol) were dissolved in water (30 mL). To this mixture a solution of N-(*t*-Boc)-4-piperidone (6.34 g, 31.86 mmol) in MeOH (30 mL) was added. The reaction mixture was stirred at 60 °C overnight. The final suspension was cooled, filtered, washed with water, and dried to afford a light brown-silverish colored solid (5.31 g, 62.0% yield); mp = 233-234 °C (dec.)

^1H NMR (DMSO-d_6 + TMS) (250 MHz): δ 10.71 (b s, 1H), 8.47 (s, 1H), 3.82-3.77 (dd, 2H), 3.09 (b s, 2H), 1.73-1.62 (dt, 2H), 1.53-1.48 (d, 2H), 1.40 (s, 9H).

^{13}C NMR (DMSO-d_6 + TMS) (62.5 MHz): δ 177.68, 156.45, 153.79, 78.85, 60.03, 32.62, 27.97

GC-MS (m/z): 212 (loss *tert*-butyl), 196, 168, 153, 141, 125, 110, 97, 82, 70, 57

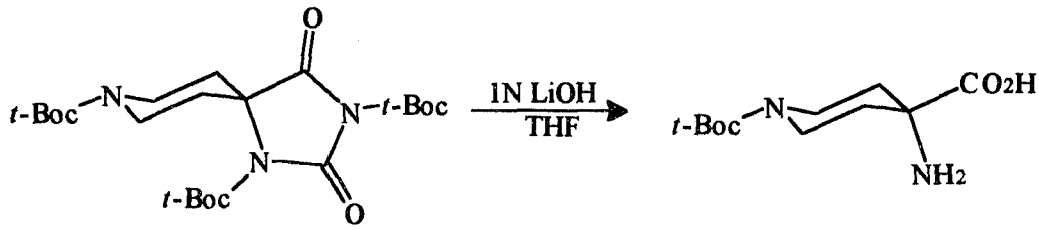


IV.2.17. N-(*t*-Boc)-4-piperidinespiro-5'-(di-*t*Boc)-hydantoin. In a 25-mL one-necked round-bottomed flask equipped with a magnetic stirring bar, N-(*t*-Boc)-4-piperidinespiro-5'-hydantoin (0.269 g, 1.00 mmol) and di-*tert*-butyl dicarbonate (0.655 g, 3.00 mmol) were suspended in dry THF (10 mL). A catalytical amount of DMAP was added and the reaction mixture was stirred for 1 h at room temperature. The final reaction mixture was concentrated under reduced pressure to give a solid. This solid was taken up in DCM (25 mL), washed with aq. 2N HCl (1 x 35 mL), conc. aq. Na_2CO_3 (25 mL), dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure to afford a light cream solid (0.469 g, 100% yield); mp = 246-247 °C.

^1H NMR ($CDCl_3$ + TMS) (250 MHz): δ 4.16-4.01 (dd, 1H), 3.4 (b t, 1H), 2.74-2.58 (dt, 1H), 1.77-1.70 (d, 1H), 1.58 (s, 9H), 1.52 (s, 9H), 1.46 (s, 9H).

^{13}C NMR ($CDCl_3$ + TMS) (62.5 MHz): δ 169.99, 154.71, 148.27, 147.50, 145.36, 87.15, 85.38, 80.13, 62.56, 29.90, 28.64, 28.24, 28.13, 27.94

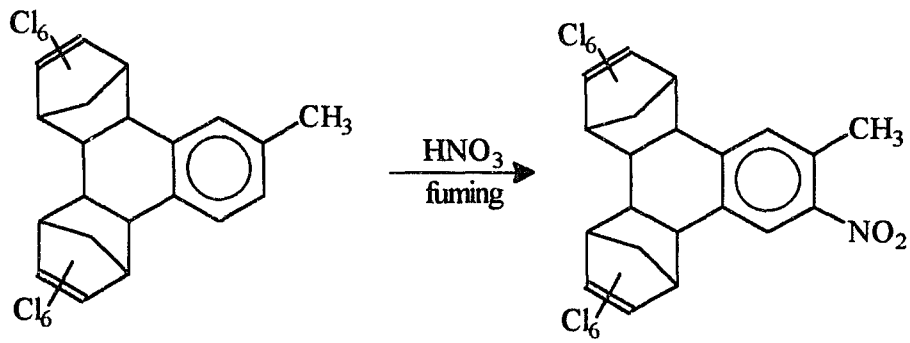
IR (cm^{-1}): 2980, 2933, 1826, 1784, 1732, 1696, 1474, 1369, 1330, 1250, 1139, 1030, 988, 947, 844, 779



IV.2.18. N-(*t*-Boc)-piperidine-4-amino-4-carboxylic acid. In a 500-mL one-necked round-bottomed flask equipped with a magnetic stirring bar, N-(*t*-Boc)-4-piperidinespiro-5'-(di-*t*-Boc)-hydantoin (1.41 g, 3.00 mmol), THF (300 mL) and aq. 1N LiOH (24 mL, 24.0 mmol) were mixed and stirred at room temperature overnight. The final reaction mixture was concentrated under reduced pressure, the pH adjusted to 7, and freeze-dried. The residue was washed with deionized water, and the remaining solid was dried to obtain an off-white solid (0.56 g, 76.5% yield).

^{1}H NMR (D_2O/NaOD + TSP) (300 MHz): δ 3.52-3.43 (m, 2H), 3.40-3.36 (m, 2H), 1.45 (s, 9H).

^{13}C NMR (D_2O/NaOD + TSP) (75 MHz): δ 217.26, 187.78, 70.08, 34.67, 30.22

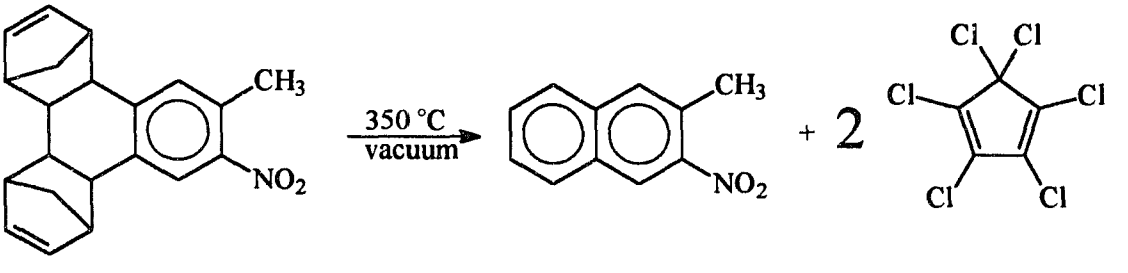


IV.2.19. 2-Methyl-3-nitro-DHA. This compound was prepared according to the procedure reported by Look.[133,134] 2-Methyl-DHA (technical grade, ALDRICH) (68.77 g, 100.0 mmol) was dissolved in DCM (1100 mL). This solution was filtered and placed

into a 5-L three-necked round-bottomed flask fitted with an addition funnel, a condenser, a thermometer, and a magnetic stirring bar. Fuming nitric acid (990 g) was added all at once to the solution with stirring. After 30 min of stirring at room temperature the final reaction mixture was then poured very carefully into 500-mL fractions into a 4-L separatory funnel containing 1 L of ice-water. The combined organic layers were washed with water (2 x 500 mL) and a 5% aq. solution of sodium bicarbonate (2 x 500 mL), dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure to afford a solid. Recrystallization in toluene gave light yellow crystals (62.23 g, 84.92% yield); mp = 249-250 °C.

^{1}H-NMR ($CDCl_3$ + TMS) (250 MHz): δ 8.41 (s, 1H), 7.73 (s, 1H), 4.03-3.96 (t, 1H), 3.57-3.54 (d, 1H), 2.65 (s, 3H).

^{13}C NMR ($CDCl_3$) (62.5 MHz): δ 147.75, 133.86, 133.80, 133.01, 132.80, 129.52, 129.40, 127.95, 125.23, 101.14, 84.52, 84.46, 82.15, 46.89, 46.67, 41.58, 41.45, 20.43

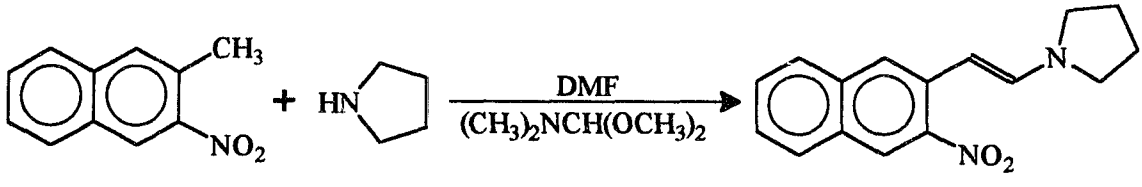


IV.2.20. 2-Methyl-3-nitronaphthalene. This compound was prepared according to the procedure reported by Look.[133,134] 2-Methyl-2-nitro-DHA (82.21 g, 0.1122 moles) was pyrolyzed at 350 °C under vacuum to get a yellow slurry. This slurry was cooled in an ice-

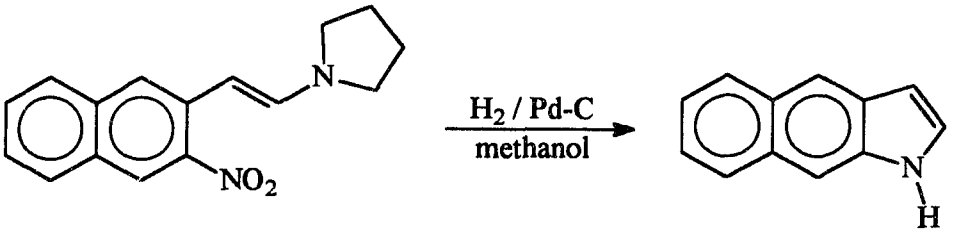
water bath, washed with cold hexanes, and crystallized from hexanes to give 2-methyl-3-nitronaphthalene (20.8 g, 99.3% yield); mp = 119-121 °C.

^{1}H-NMR ($CDCl_3$ + TMS) (250 MHz): δ 8.50 (s, 1H), 7.91-7.88 (d, 1H), 7.82-7.78 (d, 1H), 7.72 (s, 1H), 7.65-7.51 (m, 2H), 2.71 (s, 3H)

^{13}C NMR ($CDCl_3$ + TMS) (62.5 MHz): δ 147.75, 135.01, 131.22, 130.77, 129.28, 128.98, 127.05, 125.13, 20.44



IV.2.21. 2-(3-Nitro-2-naphthyl)1-(N-pyrrolidinyl)ethene. In a 25-mL one-necked round-bottomed flask fitted with a condenser and bubbler 2-methyl-3-nitronaphthalene (0.187 g, 1.00 mmol), N,N-dimethylformamide dimethyl acetal (1.19 g, 10.0 mmol), pyrrolidine (0.71 g, 10.0 mmol) and dry DMF (5 mL) were stirred and refluxed under an argon atmosphere for 6 h. Isolation of this intermediate by column chromatography over silica gel (hexanes-ethyl acetate 4:1) gave a dark brown solid. ^{1}H NMR shows clearly that starting material (2-methyl-3-nitronaphhalene) is not present and that the isolated dark brown solid is a mixture of 2-(3-nitro-2-naphthyl)1-(N-pyrrolidinyl)ethene and 2-(3-nitro-2-naphthyl)1-(N,N-dimethylamino)ethene. For practical purposes this dark brown solid was not isolated since it is only an intermediate.



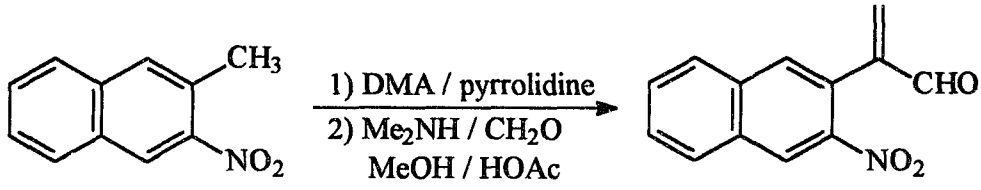
IV.2.22. Benz[*f*]indole. 2-Methyl-3-nitronaphthalene (0.374 g, 2.00 mmol) was mixed with N,N-dimethylformamide dimethyl acetal (2.38 g, 20.0 mmol), pyrrrolidine (1.42 g, 20.0 mmol), and 10 mL of dry DMF. This mixture was stirred and refluxed for 6 h under an argon atmosphere. The final reaction mixture was concentrated under reduced pressure. The dark residue was then dissolved in methanol, mixed with Pd-C (10%) and hydrogenated at 30 p.s.i. for 9 h at room temperature.

The final mixture was filtered through a celite pad and the celite pad washed with DCM until the filtrate came out colorless. The combined filtrates were concentrated under reduced pressure affording a dark green oil. This oily residue was purified by flash chromatography on a silica gel column using a solution of hexanes/DCM (1:1) to afford white flakes (0.04 g, 12% yield); mp = 185-185 °C.[120,122,119]

^{1}H-NMR (CD_3OH) (400 MHz): δ 8.02 (s, 1H), 7.86-7.79 (m, 3H), 7.44 (t, 1H), 7.27-7.19 (m, 3H), 6.56 (s, 1H).

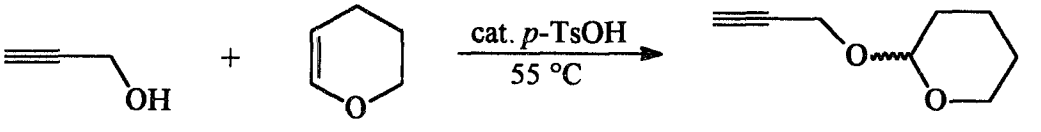
^{13}C NMR (CD_3OH) (100 MHz): δ 138.49, 131.42, 131.30, 130.09, 129.78, 128.88, 128.16, 123.96, 122.87, 118.06, 106.99, 101.46

MS: 167, 139, 83, 70



IV.2.23. α-(3-Nitro-2-naphthyl)acrolein. In a 25-mL one-necked round-bottomed flask fitted with a condenser and bubbler, 2-methyl-3-nitronaphhalene (0.935 g, 5.00 mmol), N,N-dimethylformamide dimethyl acetal (0.952 g, 8.00 mmol), pyrrolidine (0.568 g, 8.00 mmol) and dry DMF (3 mL) were stirred and refluxed under an argon atmosphere for 6 h. The final reaction mixture was concentrated under high vacuum and the residue was chromatographed over silica gel using a solution of hexanes-ethyl acetate (4:1) to give a dark brown solid. This solid was taken up in methanol and added dropwise to a mixture of 40% aq. dimethylamine (1.125 g, 10.0 mmol) , 37% aq. formaldehyde (3.24 g, 4.00 mmol), glacial acetic acid (1 g), and methanol (5 mL) at 4 °C under stirring. The mixture was stirred at 4 °C for 30 min. after which methanol was removed in vacuo. Then 20 mL of water were added dropwise at 10 °C and the suspension stirred at 4 °C for 2 h. The reaction mixture was then extracted with DCM, dried over anh. $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column using a solution of hexanes/ethyl acetate (4:1) to afford a brown solid (0.16 g, 14% yield).

^1H NMR ($CDCL_3$ + TMS) (200 MHz): δ 9.75 (s, 1, -C(O)H), 8.62 (s, 1H), 7.60-8.02 (m, 6H), 6.66 (s, 1H), 6.39 (s, 1H).

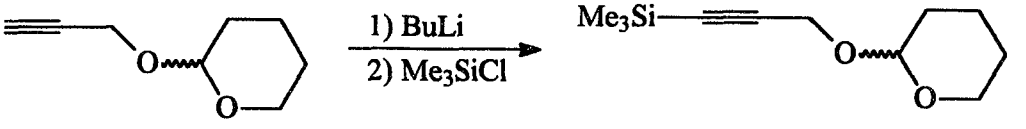


IV.2.24. Tetrahydro-2-(2-propynyloxy)-2*H*-pyran. This compound was prepared according to the procedure reported by Earl.[135] In a 100-mL three-necked round-bottomed flask equipped with a stirring bar, a thermometer, an oil-bubbler and an addition funnel, 3,4-dihydro-2*H*-pyran (46.64 g, 555.0 mmol) and few crystals of *p*-toluenesulfonic acid were stirred at 55 °C under an argon atmosphere. The addition funnel was loaded with propargyl alcohol (28.00 g, 501.0 mol) and was added dropwise under stirring at such rate that the temperature was kept at 62 °C. The reaction mixture was stirred overnight. The final yellow mixture was quenched with $NaHCO_3$ (0.1 g), stirred for 1 h, and distilled under reduced pressure. A small fraction with a bp lower than 30 °C (7 mm Hg) was followed with product (colorless liquid, 51.07 g, 72.81% yield); bp_7 = 46-47 °C.

^1H NMR ($CDCl_3$ + TMS) (250 MHz): δ 4.76 (t, 1H), 4.26-4.12 (dd, 2H), 3.81-3.73 (m, 1H), 3.50-3.45 (m, 1H), 2.38 (t, 1H), 1.76-1.45 (m, 6H).

^{13}C NMR ($CDCl_3$ + TMS) (62.5 MHz): δ 96.62, 69.64, 73.83, 61.76, 53.78, 30.05, 25.19, 18.84

GC-MS (m/z): 139, 101, 85, 67, 56, 41

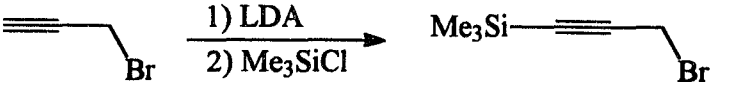


IV.2.25. 3-(Tetrahydro-2-pyranyloxy)-1-(trimethylsilyl)propyne. This compound was prepared according to the procedure reported by Hiraoka.[136] A solution of BuLi (2.5 M in hexane) (40.0 mL, 100 mmol) was added dropwise to a solution of tetrahydro-2-(2-propynyloxy)-2H-pyran (12.6 g, 90.0 mmol) in anh. diethyl ether (100 mL) at 0 °C under argon. After stirring for 30 at 0 °C, trimethylsilsyl chloride (10.86 g, 100.0 mmol) was added dropwise with vigorous stirring. The reaction mixture was stirred overnight at room temperature. The reaction was quenched by addition of sodium carbonate (0.1 g), stirred for 10 min, poured into diluted HCl and extracted with diethyl ether. The combined extracts were washed with water, dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure to give a pale yellow thick oil. This oil was vacuum-distilled (4mm Hg) to afford a colorless liquid (15.0 g, 78.6% yield).

^1H NMR ($CDCl_3$) (200 MHz): δ 4.80 (t, 1H), 4.33-4.15 (dd, 2H), 3.88-3.76 (dt, 1H), 3.56-3.45 (m, 1H), 1.86-1.49 (6H), 0.14 (s, 9H).

^{13}C NMR ($CDCl_3$) (62.5 MHz): δ 101.48, 96.67, 90.78, 61.82, 54.73, 30.18, 25.32, 18.93, -0.2

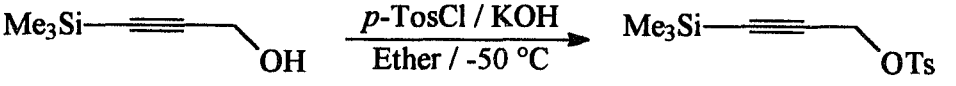
GC-MS (m/z): 211, 173, 141, 128, 111, 101, 97, 85, 73, 55, 43.



IV.2.26. 3-Bromo-1-(trimethylsilyl)prop-1-yne. This compound was prepared according to the procedure reported by Chemin.[137] In a 100-mL three-necked round-bottomed flask loaded with a magnetic stirring bar and fitted with a low-range themometer, an addition funnel and a bubbler, LDA (1.5 M in THF) (100 mL, 100.0 mmol) was placed. The reaction flask was placed in a dry ice-acetone bath to cool the LDA solution to -60 °C. To this thick solution, 3-bromo-prop-1-yne (ALDRICH, 80% wt. in toluene) (5.95 g, 50.0 mmol) in THF (10 mL) was added dropwise under stirring keeping the temperature between -55 °C and -60 °C. The reaction mixture was stirred for another 15 min. at <-70 °C. A solution of chlorotrimethylsilane (8.56 g, 78.0 mmol) in THF (10 mL) was added dropwise under stirring keeping the temperature between -65 °C and -70 °C. The reaction mixture was stirred for another 10 min. at <-70 °C. The dry ice-acetone bath was removed and the reaction mixture was allowed to reach room temperature. The reaction mixture was stirred for another h and poured into 2N aq. HCl (125 mL) under stirring. The aqueous phase was separated and extracted with ether (4 x 40 mL). The extracts were combined and dried over anh. magnesium sulfate, filtered and concentrated under vacuum to obtain a red liquid. This red liquid was fractionally distilled under high vacuum to give a colorless liquid (3.9 g, 41% yield); bp_{35} = 60-68 °C

^{1}H NMR ($CDCl_3$) δ 4.01 (s, 2H), 0.31 (s, 9H).

GC-MS (m/z): 222, 207, 191, 178, 155, 149, 133, 109, 96, 81, 73, 59, 55, 43



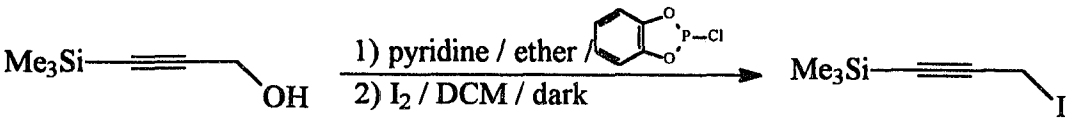
IV.2.27. 1-Tosyl-3-(trimethylsilyl)-2-propyne. This compound was prepared according to the procedure reported by Westmijze.[124] In a 100-mL three-necked round-bottomed flask equipped with a magnetic stirring bar, a low-temperature thermometer, an argon inlet, and an oil bubbler, commercially available 3-trimethylsilylpropargyl alcohol (5.13 g, 40.0 mmol) and freshly purified tosyl chloride (9.53 g, 50.0 mmol) in anh. diethyl ether were mixed under an argon atmosphere. This mixture was cooled to -50 °C and freshly powdered KOH (15.0 g, 268 mmol) was added at once under vigorous stirring. The resulting thick mixture was slowly raised to 0 °C and stirred at this temperature for 30 min. This mixture was poured onto water (200 mL), extracted with ethyl ether (3 x 50 mL), washed with water (1 x 100 mL), concentrated under reduced pressure to give a light brown oil. Crystallization from hexanes afforded colorless needles (7.93 g, 70.3 % yield); mp = 43-44 °C.

^{1}H NMR ($CDCl_3$) (250 MHz): δ 7.83-7.80 (d, 2H), 7.36-7.33 (d, 2H), 4.71 (s, 3H), 2.45 (s, 2H), 0.08 (s, 9H).

^{13}C NMR ($CDCl_3$) (62.5 MHz): δ 144.96, 133.34, 130.22, 129.79, 128.19, 127.07, 95.22, 95.01, 58.35, 21.64, 0.17

GC-MS (m/z): 267 (loss -CH3), 251, 187, 175, 159, 149, 129, 111, 91, 83, 65, 43

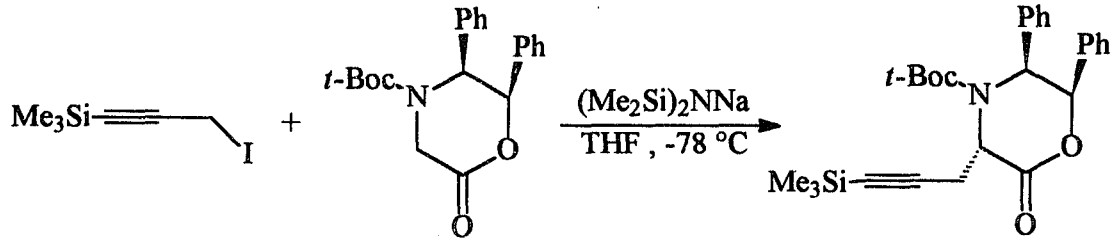
IR (cm^{-1}): 2962, 2186, 1599, 1372, 1252, 1178, 1097, 1029, 950, 846, 762, 668, 594, 555



IV.2.28. 3-Iodo-1-(trimethylsilyl)-1-propyne. This compound was prepared according to the procedure reported by Binns.[138] In a 100-mL one-necked round-bottomed flask equipped with a 25 mL pressure-equalizer addition funnel, a septum and a magnetic stirring bar, *o*-phenylene phosphorochloridite (3.49 g, 20.0 mmol) and anh. ethyl ether (20 mL) were placed under argon. A solution of anh. pyridine (1.58 g, 20.0 mmol) in anh. ethyl ether (15 mL) was cannulated into the addition funnel under argon and added dropwise under stirring at room temperature. The resulting white suspension was cooled to 0 °C. A solution of 3-trimethylsilylpropargyl alcohol (2.56 g, 20.0 mmol) in anh. ethyl ether (20 mL) was cannulated into the addition funnel under argon. This solution was added dropwise keeping the temperature of the reaction mixture at 4 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The final white suspension was filtered and the white precipitate was washed with ethyl ether (25 mL). The filtrate was concentrated under reduced pressure to give an off-white oil. This oil was dissolved in dry DCM (40 mL), and cooled with an ice-water bath under argon and iodine (2.54 g, 20.0 mmol) was added all at once. The reaction flask was wrapped with aluminum foil to keep the reaction mixture from light. The reaction mixture was allowed to warm to room temperature and stirred for 6 h. The final dark reaction mixture was transferred into a 250 mL separatory flask, and cold 20% aq. NaOH was added very carefully (2 x 50 mL). The DCM layer was washed with sat. aq. $Na_2S_2O_3$ (2 x 50 mL), brine (1 x 50 mL), dried over anh. Na_2SO_4, and passed through a silica gel pad. The pad was washed with DCM and the filtrate was concentrated under reduced pressure to afford a yellow oil (3.17 g, 88.8% yield).

^{1}H NMR ($CDCl_3$) (250 MHz): δ 3.70 (s, 2H), 0.14 (s, 9H).

GC-MS (m/z): 238, 223, 209, 195, 185, 171, 155, 127, 111, 97, 83, 55

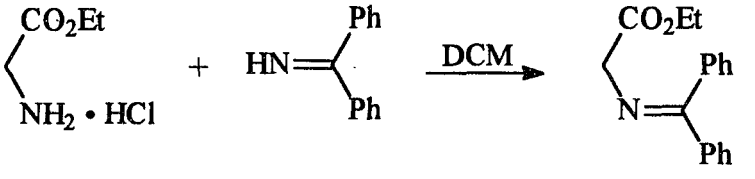


IV.2.29. *tert*-Butyl (2*R*, 3*S*, 5*S*)-(-)-6-oxo-2,3-diphenyl-5-(1-trimethylsilyl-3-propargyl) -4-morpholine-carboxylate. In a 50-mL three-necked round-bottomed flask equipped with a magnetic stirring bar, a low-temperature thermometer, a 10-mL pressure-equilized addition funnel, an argon inlet and an oil bubbler bis(trimethylsilyl)sodium amide (0.183 g, 1.00 mmol) was dissolved in dry THF (10 mL) at -78 °C with stirring under an argon atmosphere. Then *tert*-butyl (2*R*, 3*S*)-(-)-6-oxo-2,3-diphenyl-4-morpholine-carboxylate (0.388 g, 1.10 mmol) dissolved in dry THF (7 mL) was cannulated into the addition funnel under argon. The above solution was added dropwise under stirring and the resulting solution was stirred for 30 min. During this time 3-trimethylsilylpropargyl iodide (0.46 g, 1.93 mmol) in dry THF (5 mL) was cannulated into the addition funnel under argon. The iodide solution was added dropwise to the reaction mixture at -78 °C. The reaction mixture was allowed to warm to room temperature and it was stirred overnight. The final reaction mixture was poured into water (200 mL), extracted with ethyl acetate (4 x 25 mL), washed with brine, dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure to afford a light yellow solid. This solid was washed with plenty of hexanes to give white solid (0.407 g, 87.2% yield); mp = 176-177 °C.

^{1}H NMR ($CDCl_3$ + TMS) (300 MHz): δ 7.27-6.97 (m, 10H), 6.56 (t, 1H), 5.13 (m, 1H), 5.02 (m, 1H), 3.34-3.02 (dd, 2H), 1.12 (s, 9H).

^{13}C NMR ($CDCl_3$) (75 MHz): δ 169.16, 154.11, 136.77, 134.77, 128.58, 128.28, 128.09, 127.95, 127.78, 127.63, 126.51, 102.41, 189.50, 82.38, 60.87, 56.23, 28.05, 25.26

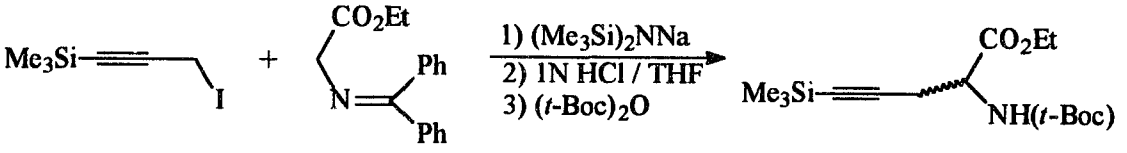
IR (cm^{-1}): 2965, 2361, 2341, 2178, 1756, 1702, 1455, 1385, 1360, 1317, 1250, 1164, 1119, 1064, 978, 844, 762, 701.



IV.2.30. Ethyl N-(diphenylmethylene)glycinate. This compound was prepared according to the procedure reported by O'Donnell.[139] Benzophenone imine (25.0 g, 0.138 moles), glycine ethyl ester hydrochloride (19.32 g, 0.138 moles), and anh. DCM (500 mL) were stirred at room temperature for 24 h in an argon atmosphere. The final reaction mixture was filtered and concentrated under reduced pressure. The residue was taken up in ether, filtered, washed with water, dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure. The resulting solid was recystallized from a solution of diethyl ether/hexanes (1:1) to afford white crystals (32.02 g, 87.01% yield); mp = 51-52 °C.

^{1}H NMR ($CDCl_3$ + TMS) (250 MHz): δ 7.68-7.64 (dd, 2H), 7.46-7.42 (m, 3H), 7.39-7.32 (m, 3H), 7.20-7.16 (dd, 2H), 4.20 (m, 4H), 1.27 (t, 3H).

^{13}C NMR ($CDCl_3$ + TMS) (62.5 MHz): 171.71. 170.52, 139.22, 135.95, 130.34, 128.68, 128.59, 127.96, 127.59, 60.74, 55.65, 14.12



IV.2.31. Ethyl 2-(N-*t*Boc)-5-trimethylsilyl-4-propynoate. In a 100-mL one-necked round-bottomed flask equipped with a magnetic stirring bar, a 25-mL pressure-equalized addition funnel, a septum, an argon inlet and an oil bubbler bis(trimethylsilyl) sodium amide (0.915 g, 5.00 mmol) was dissolved in dry THF (20 mL) with stirring under argon at -78 °C. To this solution, ethyl N-diphenylmethyleneglycinate (1.33 g, 5.00 mmol) in dry THF (20 mL) was added dropwise with stirring. After stirring for 20 min at -78 °C, 3-iodo-1-(trimethylsilyl)-1-propyne (1.36 g, 5.70 mmol) in dry THF (15 mL) was added dropwise. The reaction mixture was stirred overnight. The final dark orange mixture was poured in water (350 mL), extracted with ethyl acetate (4 x 80 mL), washed with water (2 x 100 mL), brine (1 x 100 mL), dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure. The residue was chromatographed over silica gel, using DCM as the eluent, to give a light orange oil (1.44 g). This oil was dissolved in THF and mixed with 1N HCl (25 mL). After stirring the reaction mixture for 45 min at room temperature it was concentrated under reduced pressure and the resulting residue was extracted with ethyl ether (2 x 25 mL). The aqueous phase was freeze-dried and the resulting residue was transferred into a 50 mL one-necked round-bottomed flask equipped with a magnetic stirring bar. Methanol (10 mL) was added followed by triethylamine (0.505 g, 5.00 mmol)

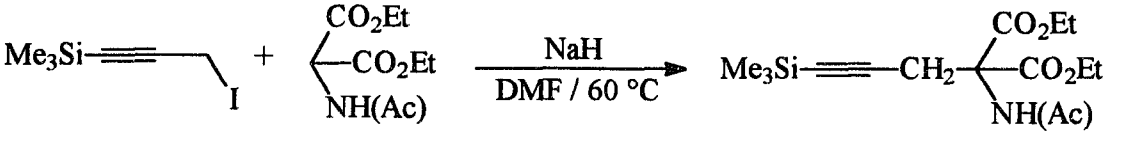
and di-*tert*-butyl carbonate (1.09 g, 5.00 mmol). A catalytic amount of DMAP was added and the reaction mixture was stirrred at room temperature overnight. The final reaction mixture was concentrated under reduced pressure. The residue was taken up in DCM (25 mL), washed with 5% aq. NH_4Cl (2 x 25 mL), sat. aq. Na_2CO_3 (1 x 25 mL), dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure to afford a light orange oil (0.548 g, 35.0% overall yield).

^1H NMR ($CDCl_3$) (250 MHz): δ 4.46-4.40 (q, 1H), 4.29-4.15 (m, 2H), 2.83-2.64 (ddd, 2H), 1.45 (s, 9H), 1.29 (t, 3H), 0.13 (s, 9H).

^{13}C NMR ($CDCl_3$) (62.5 MHz): δ 170.87, 155.29, 101.09, 88.52, 80.27, 61.80, 52.41, 28.55, 24.53, 14.42, 0.17

GC-MS (m/z): 256 (loss of *tert*-butyl), 240, 212, 198, 184, 168, 152, 140, 124, 102, 83, 73, 57

IR (cm^{-1}): 3444, 3371, 2979, 2361, 2180, 1719, 1505, 1369, 1251, 1169, 1050, 844, 761, 700, 641



IV.2.32. Diethyl 2-(N-acetamido)-5-trimethylsilyl-4-propyn-2-dicarboxylate. In a 100-mL one-necked round-bottomed flask equipped with a magnetic stirring bar, a 25-mL pressure-equalizing addition funnel, a septum, an argon intlet, and an oil bubbler, NaH (60% dispersion in oil) (0.20 g, 5.0 mmol) was placed in an argon atmosphere and washed with anh. hexanes (2 x 10 mL) to remove the oil. Once the NaH was dry, anh. DMF (10

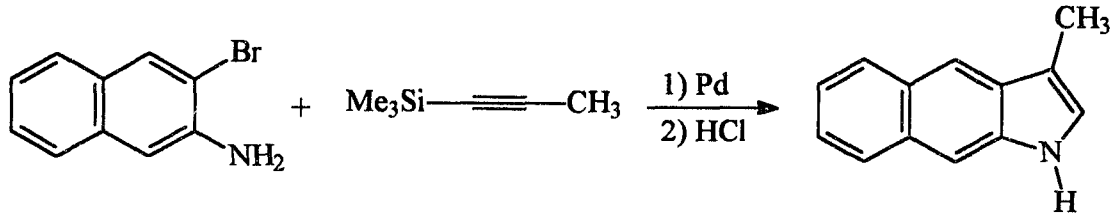
mL) was cannulated in the flask under argon, and the suspension was cooled to 4 °C with stirring. Immediately, a solution of diethyl acetamidomalonate (1.085 g, 5.00 mmol) in anh. DMF (10 mL) was cannulated into the addition funnel under argon. This solution was added to the NaH/DMF suspension dropwise with vigorous stirring. The resulting solution was stirred for another 15 min at 4 °C. Meanwhile, a solution of 3-iodo-1-(trimethylsilyl)-1-propyne (1.235 g, 5.19 mmol) in anh. DMF (5 mL) was cannulated into the addition funnel under argon. This iodide solution was added dropwise over 30 min. The resulting orange solution was stirred for 1 h at room temperature. During this time the addition funnel was replaced by a condenser, argon was flowed for a couple of min, and the reaction mixture was refluxed for 3 h.

The final reaction mixture was cooled to room temperature, quenched with 5% aq. NH_4Cl, poured onto water (180 mL), extracted with ethyl acetate (3 x 50 mL), washed with water (1 x 50 mL), dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure to afford an orange oil. This oil was taken up in ethyl acetate and chromatographed over silica gel using a solution of hexanes/ethyl acetate (3:1) to give a pale yellow oil (1.00 g, 61.6% yield).

^1H NMR ($CDCl_3$) (250 MHz): δ 6.9 (br s, N-H), 4.22 (m, 4H), 3.26 (s, 2H), 2.04 (s, 3H), 1.23 (t, 6H), 0.10 (s, 9H).

^{13}C NMR ($CDCl_3$) (62.5 MHz): δ 169.27, 166.84, 100.83, 88.34, 65.64, 63.03, 60.55, 25.57, 23.07, 14.39, 14.15, 0.14

GC-MS (m/z): 327, 312, 282, 254, 239, 223, 212, 194, 184, 174, 136, 122, 94, 73



IV.2.33. 3-Methylbenz[*f*]indole. In a 100-mL three-necked round-bottomed flask equipped with a magnetic stirring bar, a condenser, a septum, an argon inlet and an oil bubbler, 3-bromo-2-aminonaphthalene (0.221 g, 1.00 mmol), 1-trimethylsilylpropyne (0.224 g, 2.00 mmol), n-Bu_4NCl (0.278 g, 1.00 mmol), Na_2CO_3 (0.265 g, 2.50 mmol), $Pd(OAc)_2$ (22 mg, 10% mol), and PPh_3 (26 mg, 10% mol) were placed under argon. Anhydrous acetonitrile (30 mL) was cannulated into the flask with argon. The reaction flask was placed in a pre-heated oil bath (100 °C) and refluxed under stirring for 4 h. HCl gas was bubbled gently for aprox. 2 min into the dark brown reaction mixture. The resulting light brown mixture was refluxed for another h. The final mixture was poured into 3N NH_4OH (250 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with water (50 mL), 5% aq. NH_4Cl (50 mL), water (50 mL), brine (50 mL), dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure to give a dark brown solid. The brown residue was taken up in DCM and chromatographed over silica gel using hexanes/DCM (1:1). Evaporation of the solvents afforded a yellow solid (0.146 g, 80.8% yield), mp = 192-193 °C.

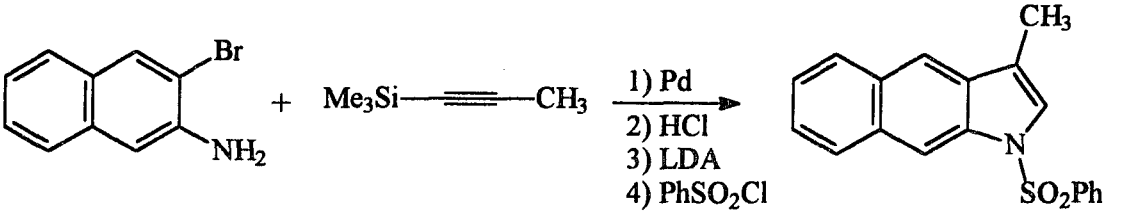
^1H NMR ($CDCl_3$ + TMS) (300 MHz): δ 8.03 (s, 1H), 7.98-7.94 (dd, 1H), 7.88-7.85 (dd, 1H), 7.71 (b s, 2H), 7.39-7.23 (m, 2H), 7.11 (s, 1H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$ + TMS) (75 MHz): δ 137.36, 130.67, 130.52, 128.46, 127.47, 125.63, 123.87, 122.65, 111.26, 106.30, 10.08

GC-MS (m/z): 181, 152, 139, 127, 90, 76, 63, 51

IR (cm^{-1}): 3414, 2924, 2854, 1634, 1446, 1084, 861, 742, 479

Elemental analysis: Calcd: C 86.15%, H 6.12%, N 7.73%. Found: C 85. 33%, H 6.11%, N 7.70%



IV.2.34. N-(Benzenesulfonyl)-3-methyl-benz[*f*]indole. In a 100-mL three-necked round-bottomed flask equipped with a magnetic stirring bar, a condenser, a septum, an argon inlet and an oil bubbler, 3-bromo-2-aminonaphthalene (0.64 g, 2.9 mmol), 1-trimethylsilylpropyne (0.648 g, 5.79 mmol), n-Bu_4NCl (0.805 g, 2.89 mmol), Na_2CO_3 (0.767 g, 7.24 mmol), $Pd(OAc)_2$ (65 mg, 10% mol), and PPh_3 (75 mg, 10% mol) were placed under argon. Anhydrous acetonitrile (40 mL) was cannulated into the flask with argon. The reaction flask was placed in a pre-heated oil bath (100 °C) and refluxed under stirring for 4 h. HCl gas was bubbled gently for aprox. 2 min into the dark brown reaction mixture. The resulting light brown mixture was refluxed for another h. The final mixture was poured into 3N NH_4OH (250 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with water (50 mL), 5% aq. NH_4Cl (50 mL), water (50 mL), brine (50 mL), dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure to give a dark brown solid.

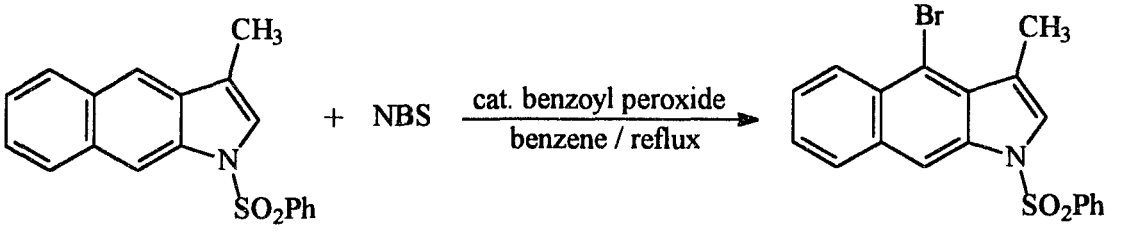
In a 100-mL one-necked round-bottomed flask equipped with a magnetic stirring bar, a 25-mL pressure-equalizing addition funnel, a septum, an argon inlet, and an oil

bubbler, solid LDA (0.321 g, 3.00 mmol) and anh. THF (15 mL) were placed under a argon. This solution was cooled to 4 °C, then the dark brown solid obtained above was taken up in anh. THF (25 mL), cannulated into the addition funnel with argon, and added dropwise, and stirred for 15 min. A solution of benzenesulphonyl chloride (0.53 g, 3.0 mmol) in anh. THF (5 mL) was cannulated in the addition funnel and added dropwise with stirring. After stirring the reaction mixture overnight, it was poured onto water (300 mL), extracted with ethyl acetate (2 x 75 mL), washed with water (1 x 100 mL), washed with brine (1 x 100 mL), dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure to give a dark brown solid. This solid was taken up in DCM and chromatographed over silica gel using a solution of hexanes/DCM (1:1) to afford a greenish colored solid (0.55 g, 60% yield); mp = 165 °C. (dec.)

^1H NMR ($CDCl_3$ + TMS) (300 MHz): δ 8.47 (s, 1H), 8.03-8.00 (d, 1H), 7.95-7.88 (m, 4H), 7.53-7.28 (m, 6H), 2.35 (s, 3H).

^{13}C NMR ($CDCl_3$ + TMS) (75 MHz): δ 133.75, 129.33, 128.51, 128.21, 126.92, 125.95, 125.39, 124.93, 117.66, 111.12, 10.06

GC-MS (m/z): 321, 180, 152, 77



IV.2.35. N-(Benzenesulfonyl)-4-bromo-3-methyl-benz[*f*]indole. In a 100-mL one-necked round-bottomed flask equipped with a magnetic stirring bar, a condenser, a

septum, an argon inlet, and an oil bubbler, N-(benzenesulfonyl)-3-methyl-benz[*f*]indole (0.558 g, 1.74 mmol), N-bromosuccinimide (0.356 g, 2.00 mmol) and a catalytic amount of benzoyl peroxide were mixed in anh. benzene (40 mL) under argon. The reaction mixture was heated to reflux and stirred for 3 h. The final reaction mixture was concentrated under reduced pressure, the solid residue was taken up in DCM and chromatographed over silica gel using a solution of hexanes/DCM (1:1) to afford an orange solid. This solid was recrystallized from ethyl acetate to give purple crystals (0.232 g, 37.7% yield);

mp = 200 °C.

^{1}H NMR ($CDCl_3$ + TMS) (300 MHz): δ 8.47 (s, 1H), 8.40-8.36 (dd, 1H), 7.99-7.95 (dd, 1H), 7.90-7.87 (s, 1H), 7.87 (s, 1H), 7.60-7.28 (m, 6H), 2.62 (s, 3H).

^{13}C NMR ($CDCl_3$ + TMS) (75 MHz): δ 137.95, 135.45, 134.03, 132.14, 129.48, 128.66, 128.02, 126.97, 126.78, 126.35, 125.97, 120.53, 114.74, 111.12, 14.22

GC-MS (m/z): 401, 399, 260, 258, 179, 151, 126, 77

IR (cm^{-1}): 1358, 1336, 1248, 1176, 1118, 1092, 946, 890, 790, 743, 724, 683, 616, 584, 559

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APPENDIX:

SUPLEMENTARY MATERIAL

Table 1. Crystal Data and Collection Parameters for Diethyl 6-(N-acetyl-3-indolyl)cyclohex-3-en-1,1-dicarboxylate.

formula	$C_{22}H_{25}NO_5$
Mr, g mol^{-1}	383.4
system	monoclinic
space group	C2/c
a, Å	32.141
b, Å	9.4594
c, Å	13.6843
α, deg	103.676
V, $Å^3$	4042.6
Z	8
D_c, g/cm^3	1.260
cryst size, mm	0.50x0.47x0.37
radiation	MoK_α
μ, cm^{-1}	0.83
temp, K	296
scan type	ω-2θ
collection range, deg	1-27.5
no. unique data	4719
no. of variables	254
R, observed	0.047
Rw	0.051
goodness of fit	2.246

Table 2. Coordinates for Diethyl 6-(N-acetyl-3-indolyl)cyclohex-3-en-1,1-dicarboxylate.

Atom	x	y	z	Beq(E2)
O1	0.31497(4)	0.2376(2)	0.1860(1)	5.07(4)
O2	0.03581(5)	0.2342(3)	-0.0218(1)	7.24(6)
O3	0.03126(5)	0.1578(2)	0.1289(1)	6.63(5)
O4	0.12960(6)	0.2995(2)	0.2750(1)	6.65(5)
O5	0.08830(5)	0.4339(2)	0.1565(1)	5.63(5)
N1	0.24345(5)	0.2384(2)	0.1225(1)	3.21(4)
C1	0.23678(6)	0.3850(2)	0.1144(2)	3.15(4)
C2	0.26601(7)	0.4955(3)	0.1318(2)	3.84(5)
C3	0.24982(8)	0.6302(3)	0.1161(2)	4.82(6)
C4	0.20635(8)	0.6552(3)	0.0834(2)	5.11(6)
C5	0.17748(7)	0.5453(3)	0.0653(2)	4.50(6)
C6	0.19251(6)	0.4071(2)	0.0806(2)	3.30(4)
C7	0.17182(6)	0.2697(2)	0.0671(2)	3.34(5)
C8	0.20329(6)	0.1733(2)	0.0924(2)	3.53(5)
C9	0.28269(6)	0.1696(3)	0.1564(2)	3.48(5)
C10	0.28173(7)	0.0127(3)	0.1530(2)	4.18(5)
C11	0.12475(6)	0.2410(3)	0.0252(2)	3.85(5)
C12	0.11782(7)	0.1238(3)	-0.0553(2)	5.14(6)
C13	0.12133(8)	-0.0216(3)	-0.0128(2)	5.79(7)
C14	0.12049(8)	-0.0499(3)	0.0795(2)	5.55(7)
C15	0.11691(7)	0.0597(3)	0.1557(2)	5.18(6)
C16	0.10106(6)	0.2027(3)	0.1091(2)	3.99(5)

(table con'd.)

C17	0.05258(7)	0.2001(3)	0.0620(2)	5.02(6)
C18	-0.01560(8)	0.1570(4)	0.0947(3)	8.3(1)
C19	-0.03329(9)	0.2999(4)	0.1040(3)	9.6(1)
C20	0.10866(6)	0.3148(3)	0.1913(2)	4.66(6)
C21	0.09126(9)	0.5506(3)	0.2279(3)	7.64(9)
C22	0.0553(1)	0.6417(4)	0.1971(3)	10.4(1)
H2	0.2959	0.4787	0.1535	4
H3	0.2689	0.7081	0.1280	6
H4	0.1962	0.7496	0.0731	6
H5	0.1476	0.5634	0.0426	5
H8	0.1988	0.0739	0.0902	4
H10a	0.3101	-0.0227	0.1730	5
H10b	0.2691	-0.0176	0.0864	5
H10c	0.2653	-0.0217	0.1973	5
H11	0.1126	0.3264	-0.0054	5
H12a	0.1387	0.1345	-0.0935	6
H12b	0.0900	0.1349	-0.0979	6
H13	0.1243	-0.0980	-0.0556	7
H14	0.1222	-0.1461	0.0998	7
H15a	0.1443	0.0726	0.1995	6
H15b	0.0974	0.0267	0.1930	6
H18a	-0.0270	0.0923	0.1344	10
H18b	-0.0234	0.1283	0.0262	10
H19a	-0.0635	0.2973	0.0815	12
H19b	-0.0256	0.3289	0.1724	12
H19c	-0.0219	0.3649	0.0641	12

(table con'd.)

H21a	0.1167	0.6024	0.2302	9
H21b	0.0917	0.5138	0.2927	9
H22a	0.0574	0.7172	0.2437	13
H22b	0.0548	0.6786	0.1323	13
H22c	0.0297	0.5900	0.1948	13

Table 3. Crystal Data and Collection Parameters for 2-(3-Indolyl)cyclohexanespiro-5'-hydantoin.

formula	$C_{16}H_{16}N_3O_2$
Mr, g mol^{-1}	282.325
system	monoclinic
space group	$P2_1/c$
a, Å	11.991
b, Å	8.3535
c, Å	15.159
β, deg	94.732
V, $Å^3$	1513.3
Z	4
D_c, g/cm^3	1.239
cryst size, mm	0.2x0.13x0.14
radiation	Mo K_α
μ, cm^{-1}	6.452
temp, K	296
scan type	ω-2θ
collection range, deg	2-75
no. unique data	3113
no. of variables	276
R, observed	0.039
Rw	0.044
goodness of fit	1.665

Table 4. Coordinates for 2-(3-Indolyl)cyclohexanespiro-5'-hydantoin.

Atom	x	y	z	B(A2)
O1	0.2805(1)	0.4491(2)	0.2464(1)	3.83(3)
O2	-0.0091(1)	0.0933(2)	0.22823(9)	3.43(3)
O3	-0.1433(1)	0.2283(2)	0.3564(1)	4.25(3)
N1	0.0829(1)	0.3410(2)	-0.0430(1)	3.85(4)
N2	0.1741(1)	0.0689(2)	0.1964(1)	2.52(3)
N3	0.1198(1)	0.2990(2)	0.2486(1)	2.88(3)
C1	0.3417(2)	0.5384(3)	0.0108(1)	3.30(4)
C2	0.3319(2)	0.6771(3)	-0.0384(2)	4.27(5)
C3	0.2335(2)	0.7120(3)	-0.0905(1)	4.70(5)
C4	0.1449(2)	0.6095(3)	-0.0959(1)	4.19(5)
C5	0.1553(2)	0.4669(3)	-0.0486(1)	3.29(4)
C6	0.2527(2)	0.4300(2)	0.0063(1)	2.71(3)
C7	0.2363(1)	0.2765(2)	0.0453(1)	2.72(4)
C8	0.1323(2)	0.2273(3)	0.0131(1)	3.59(4)
C9	0.3194(1)	0.1944(2)	0.1095(1)	2.58(3)
C10	0.3649(2)	0.0376(3)	0.0760(1)	3.43(4)
C11	0.4552(2)	-0.0326(3)	0.1405(1)	3.92(4)
C12	0.4139(2)	-0.0560(3)	0.2318(1)	3.43(4)
C13	0.3668(2)	0.0981(2)	0.2665(1)	2.86(4)
C14	0.2748(1)	0.1673(2)	0.2013(1)	2.32(3)
C15	0.2297(1)	0.3247(2)	0.2352(1)	2.69(4)
C16	0.0858(1)	0.1454(2)	0.2245(1)	2.56(3)

(table con'd.)

H2	0.388(2)	0.751(3)	-0.031(1)	5.3(5)
H3	0.228(2)	0.817(3)	-0.119(1)	6.1(6)
H4	0.080(2)	0.635(3)	-0.132(1)	5.5(5)
H5	0.405(1)	0.516(2)	0.047(1)	3.3(4)
H8	0.092(2)	0.133(2)	0.024(1)	4.6(5)
H9	0.388(1)	0.269(2)	0.120(1)	2.5(4)
H10b	0.303(2)	-0.035(2)	0.065(1)	4.4(5)
H10a	0.396(2)	0.060(2)	0.017(1)	5.0(5)
H11a	0.523(2)	0.040(2)	0.145(1)	4.3(5)
H11b	0.478(2)	-0.131(3)	0.119(1)	5.7(6)
H12a	0.353(1)	-0.140(2)	0.229(1)	4.2(5)
H12b	0.478(2)	-0.093(2)	0.270(1)	4.7(5)
H13a	0.338(1)	0.079(2)	0.325(1)	2.9(4)
H13b	0.429(1)	0.178(2)	0.272(1)	3.0(4)
H14	0.014(2)	0.325(3)	-0.073(2)	6.7(6)
H15	0.172(2)	-0.036(2)	0.182(1)	4.3(5)
H16	0.075(2)	0.375(2)	0.263(1)	5.1(5)
H17	-0.193(2)	0.179(3)	0.374(2)	10.7(9)
H18	-0.125(2)	0.171(4)	0.311(2)	14(1)

Table 5. Crystal Data and Collection Parameters for Cyclohexanespiro-5'-hydantoin.

formula	$C_8 H_{14} N_2 O_3$
Mr, g mol^{-1}	186.2
system	orthorhombic
space group	$Pna2_1$
a, Å	16.8885
b, Å	9.2407
c, Å	6.2644
V, $Å^3$	977.6
Z	4
D_c, g/cm^3	1.265
cryst size, mm	0.33x0.10x0.10
radiation	Mo K_α
μ, cm^{-1}	7.75
temp, K	296
scan type	ω-2θ
collection range, deg	2-75
no. unique data	2002
no. of variables	174
R, observed	0.034
Rw	0.038
goodness of fit	1.537

Table 6. Coordinates for Cyclohexanespiro-5'-hydantoin.

Atom	x	y	z	Beq(E2)
O1	0.23741(8)	0.6069(2)	1	5.22(4)
O2	0.40878(7)	0.5878(2)	0.4416(2)	5.35(4)
N1	0.33846(8)	0.5985(2)	0.7561(2)	3.91(3)
N2	0.27285(8)	0.6010(2)	0.4542(2)	3.63(3)
C1	0.2622(1)	0.6042(2)	0.8171(3)	3.52(4)
C2	0.3455(1)	0.5956(2)	0.5339(3)	3.70(4)
C3	0.21113(9)	0.6049(2)	0.6177(3)	2.94(3)
C4	0.1582(1)	0.4710(2)	0.6103(4)	4.11(4)
C5	0.1036(1)	0.4736(3)	0.4155(4)	4.80(5)
C6	0.0552(1)	0.6101(3)	0.4075(4)	5.15(5)
C7	0.1077(1)	0.7428(2)	0.4118(4)	4.25(4)
C8	0.1617(1)	0.7430(2)	0.6070(3)	3.83(4)
O1W	0.46712(8)	0.6133(2)	0.0270(2)	4.74(3)
H1N	0.381(1)	0.601(2)	0.854(4)	6.6(6)
H2N	0.261(1)	0.601(2)	0.328(4)	5.9(6)
H4a	0.127(1)	0.475(2)	0.750(4)	4.8(5)
H4b	0.195(1)	0.386(2)	0.622(4)	6.3(5)
H5a	0.069(1)	0.395(2)	0.416(4)	5.3(5)
H5b	0.139(1)	0.466(2)	0.291(3)	5.1(5)
H6a	0.019(1)	0.609(2)	0.548(5)	9.4(8)
H6b	0.017(1)	0.617(2)	0.282(4)	7.2(6)
H7a	0.073(1)	0.829(2)	0.401(4)	6.2(6)

(table con'd.)

H7b	0.147(1)	0.743(2)	0.281(3)	6.3(6)
H8a	0.200(1)	0.830(2)	0.606(4)	5.2(5)
H8b	0.130(1)	0.741(2)	0.746(3)	4.3(4)
H1W	0.506(1)	0.552(3)	0.005(5)	8.9(7)
H2W	0.446(1)	0.602(2)	0.167(4)	7.4(7)

Table 7. Crystal Data and Collection Parameters for 3-Methyl-2-nitro-naphthalene-bis(hexachlorocyclopentadiene) adduct.

formula	$C_{22}H_{17}NO_2Cl_{12}$
Mr, g mol^{-1}	824.9
system	triclinic
space group	$P\bar{1}$
a, Å	10.068
b, Å	10.145
c, Å	17.739
α, deg	103.336
β, deg	92.912
γ, deg	111.119
V, $Å^3$	1626.6
Z	2
D_c, g/cm^3	1.684
cryst size, mm	0.45x0.50x0.68
radiation	Mo K_α
μ, cm^{-1}	10.6
temp, K	294
scan type	ω-2θ
collection range, deg	1-27.5
no. unique data	7464
no. of variables	396
R, observed	0.045

(table con'd.)

Rw	0.053
goodness of fit	2.822

Table 8. Coordinates for 3-Methyl-2-nitro-naphthalene-bis(cyclohexachloropentadiene) adduct.

Atom	x	y	z	B(A2)
CL1	0.55119(9)	0.22159(9)	0.18315(5)	4.50(2)
CL2	0.2187(1)	0.20364(9)	0.15125(5)	4.84(2)
CL3	0.09973(9)	0.26248(9)	0.32940(6)	5.00(2)
CL4	0.3553(1)	0.30772(8)	0.46573(4)	4.22(2)
CL5	0.5465(1)	0.47944(8)	0.33994(5)	4.37(2)
CL6	0.64720(9)	0.27238(9)	0.38112(6)	4.51(2)
CL7	0.2581(1)	-0.06713(9)	0.50509(5)	4.67(2)
CL8	0.4280(1)	-0.2288(1)	0.38820(7)	6.07(3)
CL9	0.1922(1)	-0.45160(9)	0.22159(6)	5.28(2)
CL10	-0.1236(1)	-0.4308(1)	0.24279(6)	5.05(2)
CL11	-0.0026(1)	-0.40632(9)	0.42867(6)	5.95(3)
CL12	-0.09383(9)	-0.1755(1)	0.41656(5)	4.95(2)
O1	-0.1227(4)	-0.4198(4)	0.0024(2)	6.0(1)
O1'	0.242(2)	-0.322(2)	-0.051(1)	15.2*
O2	0.0100(5)	-0.2833(5)	-0.0615(2)	7.9(1)
O2'	0.401(2)	-0.168(2)	-0.0107(9)	11.8*
N	-0.0172(4)	-0.3251(4)	-0.0037(2)	5.67(9)
C1	0.3909(3)	0.0336(3)	0.2693(2)	2.47(6)
C2	0.3378(3)	0.0613(3)	0.3502(2)	2.49(6)
C3	0.1855(3)	-0.0373(3)	0.3585(2)	2.45(6)
C4	0.0790(3)	-0.1387(3)	0.2827(2)	2.58(6)

(table con'd.)

C5	0.1377(3)	-0.1412(3)	0.2064(2)	2.49(6)
C6	0.0425(3)	-0.2200(3)	0.1375(2)	3.12(7)
C7	0.0935(4)	-0.2461(3)	0.0664(2)	3.60(7)
C8	0.2386(4)	-0.2005(3)	0.0626(2)	3.50(7)
C9	0.3325(3)	-0.1178(3)	0.1310(2)	3.10(7)
C10	0.2836(3)	-0.0814(3)	0.2020(2)	2.39(6)
C11	0.4357(3)	0.1878(3)	0.2527(2)	2.80(6)
C12	0.2988(3)	0.2150(3)	0.2399(2)	3.00(7)
C13	0.2528(3)	0.2373(3)	0.3085(2)	2.97(6)

Table 9. Crystal Data and Collection Parameters for 3-Trimethylsily-2-propynyl *p*-toluenesulfonate.

formula	$C_{13}\ H_{18}\ S\ Si\ O_3$
Mr, g mol^{-1}	282.4
system	monoclinic
space group	$P2_1/c$
a, Å	11.1390
b, Å	12.9734
c, Å	12.0033
β, deg	114.543
V, $Å^3$	1577.9
Z	4
D_C, g/cm^3	1.189
cryst size, mm	0.50x0.37x0.18
radiation	Mo K_α
μ, cm^{-1}	2.68
temp, K	296
scan type	ω-2θ
collection range, deg	1-25
no. unique data	2773
no. of variables	191
R, observed	0.047
Rw	0.041
goodness of fit	1.652

Table 10. Coordinates for 3-Trimethylsilyl-2-propynyl *p*-toluenesulfonate.

Atom	x	y	z	Beq(E2)
S	0.50756(6)	0.16824(5)	0.96577(6)	5.00(2)
Si	0.00909(7)	0.25924(6)	0.54596(6)	5.39(2)
O1	0.3877(2)	0.0949(2)	0.9355(2)	5.59(6)*
O2	0.5825(2)	0.1384(2)	0.9020(2)	6.79(7)*
O3	0.5710(2)	0.1690(2)	1.0976(2)	6.70(7)*
O1'	0.4390(5)	0.0938(4)	0.8445(5)	5.1(1)*
O2'	0.6385(5)	0.1695(5)	0.9788(7)	8.0(2)*
O3'	0.4687(6)	0.1303(5)	1.0585(5)	6.6(2)*
C1	0.3176(3)	0.0531(2)	0.8128(3)	6.90(9)
C2	0.2192(2)	0.1217(2)	0.7266(2)	5.48(7)
C3	0.1375(2)	0.1751(2)	0.6555(2)	5.55(7)
C4	0.0874(3)	0.3383(3)	0.4665(3)	8.04(9)
C5	-0.0541(3)	0.3423(3)	0.6343(3)	8.1(1)
C6	-0.1216(3)	0.1753(3)	0.4383(3)	7.69(9)
C7	0.4380(2)	0.2902(2)	0.9164(2)	4.29(6)
C8	0.4475(2)	0.3359(2)	0.8176(2)	5.06(6)
C9	0.3903(2)	0.4319(2)	0.7802(2)	5.75(7)
C10	0.3247(2)	0.4813(2)	0.8391(2)	5.62(7)
C11	0.3173(3)	0.4333(2)	0.9379(2)	6.53(7)
C12	0.3729(2)	0.3376(2)	0.9771(2)	5.66(7)
C13	0.2630(3)	0.5856(2)	0.7955(3)	9.0(1)
H1a	0.2742	-0.0083	0.8188	8*

(table con'd.)

H1b	0.3806	0.0372	0.7810	8*
H1c	0.3129	-0.0123	0.7755	8*
H1d	0.3010	0.0451	0.8838	8*
H4a	0.1601	0.3737	0.5256	10
H4b	0.0254	0.3865	0.4144	10
H4c	0.1169	0.2949	0.4191	10
H5a	-0.1125	0.3920	0.5811	10
H5b	0.0175	0.3762	0.6974	10
H5c	-0.0999	0.3013	0.6696	10
H6a	-0.0862	0.1366	0.3918	9
H6b	-0.1929	0.2164	0.3850	9
H6c	-0.1521	0.1297	0.4828	9
H8	0.4924	0.3024	0.7755	6
H9	0.3968	0.4642	0.7118	7
H11	0.2728	0.4667	0.9803	8
H12	0.3660	0.3051	1.0452	7
H13a	0.2430	0.6163	0.8573	11
H13b	0.1842	0.5777	0.7230	11
H13c	0.3230	0.6281	0.7789	11
H13d	0.1737	0.5844	0.7850	11
H13e	0.2664	0.6015	0.7196	11
H13f	0.3101	0.6364	0.8545	11

Table 11. Crystal Data and Collection Parameters for 2-(Trimethylsilyl)-3-methyl-3*H*-benz[*f*]indolyl-3-hydroperoxide.

formula	$C_{16}H_{19}SiNO_2$
Mr, g mol^{-1}	285.4
system	monoclinic
space group	$P2_1$
a, Å	9.7343
b, Å	17.0747
c, Å	9.7644
β, deg	96.403
V, $Å^3$	1612.8
Z	4
D_c, g/cm^3	1.176
cryst size, mm	0.23x0.25x0.38
radiation	Cu K_α
μ, cm^{-1}	12.8
temp, K	295
scan type	ω-2θ
collection range, deg	2-75
no. unique data	6562
no. of variables	369
R, observed	0.041
Rw	0.048
goodness of fit	2.146

Table 12. Coordinates for 2-(Trimethylsilyl)-3-methyl-3*H*-benz[*f*]indolyl-3-hydroperoxide.

Atom	x	y	z	B(Å^2)
Si1A	0.57600(6)	1	0.23086(7)	4.31(1)
O1A	0.5467(2)	0.88827(9)	-0.0659(2)	4.07(3)
O2A	0.4903(2)	0.9637(1)	-0.1125(2)	4.88(4)
N1A	0.3159(2)	0.9352(1)	0.1602(2)	3.58(3)
C1A	0.4455(2)	0.9287(1)	0.1430(2)	3.43(4)
C2A	0.4719(2)	0.8621(1)	0.0434(2)	3.41(4)
C3A	0.3257(2)	0.8358(1)	-0.0022(2)	3.30(4)
C4A	0.2380(2)	0.8807(1)	0.0729(2)	3.28(4)
C5A	0.2733(2)	0.7797(1)	-0.0903(2)	3.98(4)
C6A	0.1274(2)	0.7669(1)	-0.1106(2)	4.01(5)
C7A	0.0668(3)	0.7091(2)	-0.2016(3)	5.52(6)
C8A	-0.0731(3)	0.6967(2)	-0.2171(3)	6.18(7)
C9A	-0.1584(3)	0.7438(2)	-0.1467(3)	6.10(7)
C10A	-0.1040(3)	0.8008(2)	-0.0596(3)	5.10(6)
C11A	0.0402(2)	0.8135(1)	-0.0362(2)	3.91(4)
C12A	0.0982(2)	0.8712(1)	0.0569(2)	3.81(4)
C13A	0.5616(2)	0.7977(2)	0.1134(3)	4.78(5)
C14A	0.7462(3)	0.9897(2)	0.1629(3)	7.50(8)
C15A	0.5003(4)	1.0978(2)	0.1922(3)	6.61(8)
C16A	0.5919(3)	0.9785(2)	0.4173(3)	5.90(7)
H2OA	0.408(3)	0.950(2)	-0.169(3)	7.5(8)

(table con'd.)

H5A	0.3331	0.7487	-0.1385	5
H7A	0.1240	0.6781	-0.2528	7
H8A	-0.1117	0.6561	-0.2757	8
H9A	-0.2555	0.7360	-0.1596	7
H10A	-0.1642	0.8327	-0.0135	6
H12A	0.0408	0.9026	0.1072	4
H131A	0.5184	0.7770	0.1881	6
H132A	0.5730	0.7572	0.0489	6
H133A	0.6494	0.8186	0.1468	6
H141A	0.8099	1.0259	0.2082	9
H142A	0.7799	0.9379	0.1790	9
H143A	0.7357	1.0000	0.0666	9
H151A	0.5609	1.1368	0.2335	8
H152A	0.4874	1.1054	0.0952	8
H153A	0.4136	1.1013	0.2279	8
H161A	0.6568	1.0133	0.4647	7
H162A	0.5044	0.9850	0.4505	7
H163A	0.6225	0.9260	0.4327	7

Table 13. Crystal Data and Collection Parameters for N-Benzenesulfonyl-4-bromo-3-methyl-benz[*f*]indole.

formula	$C_{19}H_{14}NO_2BrS$
Mr, g mol^{-1}	400.3
system	triclinic
space group	$P\bar{1}$
a, Å	8.1400
b, Å	10.0587
c, Å	10.8863
α, deg	89.927
β, deg	110.459
γ, deg	96.846
V, $Å^3$	828.2
Z	2
D_c, g/cm^3	1.602
cryst size, mm	0.40x0.23x0.20
radiation	Mo K_α
μ, cm^{-1}	25.8
temp, K	299
scan type	ω-2θ
collection range, deg	1-27.5
no. unique data	3826
no. of variables	217
R, observed	0.050

(table con'd.)

Rw	0.040
goodness of fit	1.604

Table 14. Coordinates for N-(Benzenesulfonyl)-4-bromo-3-methyl-benz[*f*]indole.

Atom	x	y	z	B(Å2)
Br	0.11505(5)	0.28001(4)	0.48213(4)	5.852(9)
S	0.6093(1)	0.85632(8)	0.74110(8)	3.90(2)
O1	0.6259(3)	0.9370(2)	0.6380(2)	4.72(6)
O2	0.7559(3)	0.8506(2)	0.8586(2)	5.26(6)
N1	0.5495(3)	0.6992(2)	0.6819(2)	3.78(6)
C1	0.5638(4)	0.5918(3)	0.7665(3)	4.42(8)
C2	0.4459(4)	0.4857(3)	0.7084(3)	4.11(8)
C3	0.3424(4)	0.5238(3)	0.5782(3)	3.64(7)
C4	0.4071(4)	0.6584(3)	0.5650(3)	3.27(6)
C5	0.2058(4)	0.4607(3)	0.4730(3)	3.79(7)
C6	0.1311(4)	0.5269(3)	0.3559(3)	4.03(7)
C7	-0.0063(4)	0.4636(4)	0.2455(3)	4.96(9)
C8	-0.0730(5)	0.5335(4)	0.1344(4)	6.3(1)
C9	-0.0071(5)	0.6677(4)	0.1271(4)	6.1(1)
C10	0.1246(4)	0.7303(4)	0.2315(3)	4.72(9)
C11	0.1991(4)	0.6634(3)	0.3486(3)	3.75(7)
C12	0.3395(4)	0.7285(3)	0.4548(3)	3.84(7)
C13	0.4345(5)	0.3538(4)	0.7726(4)	5.7(1)
C14	0.4308(4)	0.8967(3)	0.7816(3)	3.78(7)
C15	0.4130(5)	0.8502(4)	0.8951(3)	5.22(9)
C16	0.2688(5)	0.8802(4)	0.9265(4)	6.6(1)
C17	0.1513(5)	0.9560(4)	0.8459(4)	6.7(1)

(table con'd.)

C18	0.1701(5)	1.0013(4)	0.7342(4)	6.3(1)
C19	0.3126(4)	0.9729(3)	0.6987(4)	4.98(9)
H1	0.6464	0.5942	0.8536	5
H7	-0.0525	0.3728	0.2482	6
H8	-0.1657	0.4901	0.0606	8
H9	-0.0549	0.7142	0.0491	7
H10	0.1680	0.8212	0.2261	6
H12	0.3862	0.8187	0.4502	4
H13a	0.5131	0.3620	0.8612	7
H13b	0.4659	0.2866	0.7266	7
H13c	0.3170	0.3293	0.7703	7
H15	0.4970	0.7986	0.9512	6
H16	0.2528	0.8477	1.0040	8
H17	0.0546	0.9774	0.8684	8
H18	0.0855	1.0530	0.6788	8
H19	0.3268	1.0050	0.6204	6

VITA

Guillermo A. Morales was born October 26, 1966 in Monterrey, N. L., Mexico.

He graduated from Universidad Autónoma de Nuevo León, Monterrey, Mexico, in August 1989, where he received his B.S. degree in Chemistry.

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DOCTORAL EXAMINATION AND DISSERTATION REPORT

Candidate: Guillermo Morales

Major Field: Chemistry

Title of Dissertation: Synthesis of Benz[*f*]tryptophan and Constrained Amino Acid Derivatives as Fluorescence Probes

Approved:

Mark L. McLaughlin
Major Professor and Chairman

Dean of the Graduate School

EXAMINING COMMITTEE:

Steven A. Soper

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Date of Examination:

June 7, 1995